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FAT INGESTION, BLOOD COAGULATION AND ATHEROSCLEROSIS

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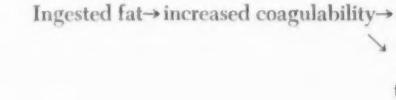
The incidence of atherosclerosis is said to be increasing, but it is not known why. Many etiological factors have been suggested with varying degrees of plausability. Atheromatous plaques contain lipids and some sufferers die from cerebral or coronary thrombosis. A study of blood lipids and blood coagulation may, therefore, be relevant. This article will consider mainly some changes in the blood after a fatty meal and discuss whether these changes may be causally related to atherosclerosis.

The association between the fat consumption of a community and the incidence of coronary disease is likely, although Morris[41] has pointed out that some epidemiological work does not support this conclusion. Ahrends, Blankenhorn and Tsaltas[1], Malmros and Wigand[38], Kinsell and Michaels[34] and Bronte Stewart *et al.*[14] have all shown that the ingestion of some saturated fats for a considerable time produced marked changes in the fasting serum lipid levels such as a rise in cholesterol and β lipoproteins. An association between increased plasma β lipoproteins and atherosclerosis is probable (Gofman *et al.*[25]), but is perhaps not firmly established: indeed, it will be difficult to incriminate any one substance, since the lipid constituents of plasma often vary in parallel. For example, the β lipoprotein and cholesterol levels in Bronte-Stewart's patients always changed in parallel. However, it can be said that with a high intake of some saturated fats the plasma cholesterol and β lipoprotein levels are raised and perhaps this predisposes to atheroma. Duguid[19] showed that intravascular mural clots became covered with vascular endothelium and were thus incorporated in the subendothelial layer of the artery, and might then become the origin of an atheromatous plaque. Fullerton, Davie and Anastasopoulos[24] claimed that there was a shortening of the clotting time of whole blood in silicone glassware after a large fatty meal. Thus, it seemed possible that the association between fat ingestion and coronary disease might be due to the increased coagulability of the blood after a fatty meal leading to the formation of mural clots which develop into atheromatous plaques. This hypothesis may be illustrated diagrammatically:



This hypothesis is simple and straightforward, and, if true, of great practical importance. It is, therefore, necessary to scrutinize the facts relating to the changes in the blood after a fatty meal and the justification for the conclusions implicit in the above hypothesis.

A Consideration of the Problem. FAT. The classes of lipids that may be relevant include at least the following: free fatty acids, mono-, di-, and triglycerides, phospholipids, lipoproteins, and possibly the proteo-lipids. The precise identification of any one constituent in plasma or in a fatty meal is a great labor and frequently the methods are not yet available to give all the information. For example, for the full identification of a lecithin, it would be necessary to know which fatty acids are in the α and β positions and the orientation of these related to the phosphatyl choline group. Naturally occurring lecithins are most unlikely to be homogeneous and probably contain a mixture of lecithins with fatty acids of chain length C_6-C_{24}. These fatty acids must be defined not only by their chain length, but also by the number of double bonds, and whether they are in the more active cis or the less active trans form. It would also be necessary to know the physical state of the lecithin molecules, whether they are dissolved, and if so, in what, or polymerized, or whether they have formed micelles or mixed micelles with some other lipid.

Clearly the weight and composition of the ingested lipids should be known. Apart from triglycerides, natural oils may contain small quantities of potentially active lipids such as sterols, branched chain fatty acids, and the like. It should be remembered that the iodine value of a mixed natural oil can only give the average degree of unsaturation (number of double bonds in the fatty acids), and thus would fail to indicate the presence of a small fraction of highly unsaturated and possibly active fatty acid, if present together with a high concentration of a more fully saturated fatty acid. The separation of the lipids, one from another, is still difficult; when dealing with samples isolated from natural sources, it is important to know the extent to which the sample might be contaminated by related substances that might be active in the test under consideration.

In the examination of the pre- and post-prandial plasma, the proportion of triglyceride transported in the form of chylomicra should be measured. These large (up to 1 μ in diameter) bodies composed largely of insoluble tri-glyceride and a little phospholipid, clearly might have a different effect from that of the same tri-glyceride if it could be "solubilized." The opacity of a plasma is only a rough measure of the number of large chylomicra. An increase in particulate fat producing opacity is usually, but not always, accompanied by an increase in nonparticulate fat; while, if the plasma remains clear after a meal, there may or may not have been an increase in soluble fat.

Changes in apparently "inactive" lipids should also be measured, since the solubility and other physicochemical properties of many lipids, especially the phospholipids, are frequently grossly altered by the presence of other lipids. For example, Rapport[56] observed that lecithin was inactive and phosphatidyl-serine was only moderately active in a clotting system. These two substances were mixed in a fat solvent, dried and suspended in water, and the mixture was found to be highly active.

Following a fatty meal, the plasma lipid pattern might alter for the following reasons: the intrinsic lipid constituents of the plasma may change in order

to transport the ingested lipid. Some or all, of the ingested lipid might pass into the blood stream unchanged. The ingested lipid may be changed in its passage through the intestinal wall or in the liver or elsewhere.

Much of the desired information outlined above is still unobtainable, since the separation and identification of lipids, especially when present in small quantities and in the presence of other lipids, is extremely difficult. But the criteria have been enumerated to emphasize the complexity of the problem and the relative paucity of the information available at present.

THE COAGULABILITY OF THE BLOOD. O'Brien[44] has shown that in the presence of platelets and a glass surface, no *in vitro* coagulation changes were apparent after a fatty meal; this has recently been emphasized by Hall[30]. Thus, it is important to consider what is meant by "increased coagulability," and how it could be measured.

Studies *in vivo* are few and difficult. Jewell and others[71] found that thromboses in the ear veins of rabbits produced by the injection of monoethanolamine oleate were largely prevented when the animal was given ethyl biscoumacetate, but that heparin did not significantly reduce the incidence of thrombosis. Wessler and Morris[72] isolated segments of undamaged vein in the dog and studied the rate of coagulation in this stationary blood. They found that a fraction from serum containing convertin (SPCA) greatly accelerated the rate of clotting and that this effect was often inhibited by heparin, but not at all by large doses of dicoumarin.

Blood coagulation can be studied from the point of view of electric potential. Sawyer, Pate and Weldon[59] reported some experiments that could have other interpretations, but claimed that a positively charged electrode placed on the outside of a blood vessel reversed the negative charge on the intima and attracted the negatively charged platelets, thereby producing a mural thrombus, histologically indistinguishable from that found naturally. They also alleged that severe mechanical crushing of the vessel produced an area of positive charge. Lovelock and Porterfield[36] suggest that if the blood vessels are lined by mucoitin, the strong negative charge of this water-wettable surface is important; and they have shown that the hydrophilic, but strongly negatively charged, surface of sulphonated polystyrene greatly delays the clotting of shed blood. It can be studied *in vitro* from the point of view of physical chemistry and surface chemistry; but very few such studies have been carried out. Lastly, it can be studied by the classical methods of the coagulationist. These studies are numerous and concerned chiefly with coagulation defects, but it is still not known what initiates the coagulation process, nor why blood does not clot in the blood vessels; in other words, hypocoagulability has been extensively investigated in the laboratory, but the study of hypercoagulability, recently reviewed in the British Medical Journal[13], is in its infancy.

At the present time we cannot measure increased coagulability *in vivo*. How then is normal clotting, even in the test tube, to be defined and characterized? It must be qualitatively and quantitatively normal at all stages, that is, there should be a normal sequence of events involving the appearance and disappearance of any identifiable substances in normal quantities and at the normal time, since the efficiency of enzyme systems is measured by the rate of their activity. It is tentatively suggested that an over-all picture might be obtained by the following tests:

First, simple clotting times of blood in glass and silicone-treated glassware. These test the efficiency of the initiation of blood clotting, but tell nothing of the sequence of events thereafter except that the clot is formed. Secondly, the thrombin generation test on natural blood or on citrated platelet-rich plasma, which measures both the rate of formation and the quantity of thrombin formed (provided that the antithrombic activity is normal). Thirdly, the prothrombin consumption test which is a measure of the degree of completeness of the whole process: and fourthly, a fibrinogen assay.

All *in vitro* clotting tests are, in a sense, unnatural. An even more artificial test is the Russell viper venom accelerated clotting time (the Stypven time). To the plasma under test is added a volume of Russell viper venom (Stypven, Burroughs, Welcome & Co.) at optimal dilution and the plasma is recalcified. This addition shortens the clotting time of the plasma from minutes to about 20 seconds. This time is referred to as the "Stypven time." It is thought that the venom in the presence of Factor V and platelet lipid forms a "thromboplastin" indistinguishable from intrinsic thromboplastin, when thromboplastin is defined as the enzyme that converts prothrombin to thrombin. Recently, there is some evidence that a serum factor may also be involved (Hougie[32a]). If the platelet lipid is removed, this system then becomes extremely sensitive to the presence of minute quantities of any phospholipid or fatty acid that can substitute in this test for platelet lipid. For example, O'Brien[48] has shown that the addition of as little as 0.1γ of phosphatidyl-ethanolamine (P.E.) per ml. to a suitable modification of this test shortened the Stypven time. Thus, providing the other prerequisites known and unknown in the plasma remain constant, this test can be considered as a method of biological assay of "active" phospholipids; and Stypven times could, under suitable conditions, be converted into "P.E.-equivalents: μg. per ml." (O'Brien[48]). This concept does not imply that there is a fundamental difference between this test and other more orthodox clotting tests, many of which can be modified to measure the quantity of a given reactant. Such tests, like the Stypven test, are clearly far removed from physiological coagulation.

A Survey of the Present Factual Position. MOSTLY COAGULATION. With the above criteria in mind, it is now possible to review the work on the relation of ingested fat to blood coagulation. Duncan and Waldron[21] and Waldron, Beidelman and Duncan[66] gave a "meal" containing 60 ml. of 20% cream to 100 volunteers; they reported a shortening in the postprandial silicone clotting time, but these results were subsequently challenged on technical grounds, although they have since confirmed and extended these findings (Waldron and Duncan[67]). Tullock, Overman and Wright[64] then claimed that 66 ml. of cream with 18% fat produced no change in the silicone clotting time; but a reassessment of their figures (15 and 54) clearly show that, in fact, there was a highly significant statistical difference in the postprandial clotting times, compared with the fasting times. Fullerton, Davie and Anastasopoulos[24] reported a pronounced shortening of the whole blood silicone clotting time in 15 subjects after the ingestion of 85 gm. of fat, consisting of bacon and eggs and butter. O'Brien[44] gave 20 volunteers of both sexes, aged 20 to 52 years, 50 gm. of animal fat. He emphasized the variability of the whole blood silicone clotting time, but showed a significant shortening. He also reported a slight

improvement in the thrombin generation test of citrated platelet-poor plasma and confirmed Fullerton's observation that there was a shortening of the Stypven time. He was unable to show that these changes were related to the changes in the total ether extractable fatty acids in the plasmas, or to the opacity of the plasma. He found little evidence that chylomicra played an important part in these changes, although, it has been shown by Poole[51] that under some conditions, chylomicra can accelerate blood coagulation.

Merskey[40] and Merskey and Nossel[40a] in an extensive and carefully controlled study of the effect of meals containing usually 100 gm. of fat, found no change 4 hours after the meal in the following tests: the silicone clotting time of whole blood, the clotting time of plasma, the thrombin generation and the thromboplastin generation tests. Thus, there is no general agreement that there is an acceleration of the whole blood clotting time. The poor reproducibility of this test suggests that there are numbers of unknown and uncontrollable variables, and so perhaps this lack of agreement is not surprising. The test is probably suitable only for showing some fairly gross differences in coagulability of the blood. It is because of this variability and disagreement using the silicone clotting test, that some workers have forsaken it (although Waldron and Duncan[67] recommend it) for the Stypven time. This latter test is highly reproducible and it is generally agreed that there is considerable and consistent shortening after a fatty meal. The interpretation of changes in so artificial a system will be discussed below.

O'Brien[48] has since shown that the shortening of the Stypven time is similar after meals consisting of 50 gm. of butter, 50 gm. of margarine and 50 gm. of cooking fat. The Stypven time which is very sensitive to the presence of P.E. (phosphatidyl-ethanolamine) in the plasma is shortened after eating two eggs containing only 10 gm. of fat, including 3 gm. of phospholipid and 0.6 gm. of P.E.; as much as, or more than after the ingestion of 50 gm. of triglyceride. He concluded that a postprandial increase in the plasma of substances like P.E. might be an important cause of the coagulation changes.

Maclagan and Billimoria[37] reported a shortening of the Stypven time in 7 volunteers after eating 2 oz. (46 gm.) of butter, but, unlike O'Brien[48], found no change following the ingestion of margarine; but neither author specifies the composition of the margarine, which varies widely. Maclagan also isolated an extract from butter which he thinks contains a galactoside of phosphatidyl-ethanolamine. This extract, still impure, will accelerate the Stypven time of platelet-poor plasma, at least as much, or more than the equivalent weight of the sample of phosphatidyl-ethanolamine studied by O'Brien[48]. The observation that the acceleration of the clotting time might be due to a substance other than P.E. is important, and has been extended by O'Brien[46a]. He has shown that phosphatidyl-serine and inositol phosphatide and a mixture of egg lecithin and cardiolipin (Pangborn[49]) will also produce maximal shortening of the Stypven clotting time, although Poole and Robinson[55] report that phosphatidyl-serine and phosphatidyl inositide are inactive. It seems, therefore, that the postprandial acceleration of the Stypven clotting time could possibly be due to the presence in the plasma of any one of a number of identified or, as yet, unidentified phospholipids.

Keys *et al.*[33] also compared the effects of giving different fats. They gave 12 males, aged 35 to 60 years,

TABLE 1.—THE EFFECT ON THE STYPVEN TIME OF MEALS OF FAT OF DIFFERENT DEGREES OF SATURATION AND CHAIN LENGTH

			Stypven Time			*Total Plasma Fatty Acid*		
	Chain Length	*Iodine Value*	*Fasting in Seconds*	*Lipemic in Seconds*	*% Difference*	*Fasting mg./100 ml.*	*Lipemic mg./100 ml.*	*% Difference*
50 gm. cod liver oil	16–20°	165	48	25	48	255	399	56
50 gm. soya bean oil	18°	126	56	34	39	340	415	22
50 gm. triolein	18	90	22	17	23	306	321	7
50 gm. hardened cod liver oil	16–20°	68	55	33	40	319	404	27
50 gm. butter etc.†	16–18°	30	88	64	27	–	–	–
50 gm. coconut oil (48% trilaurin)	12–20°	8	57	65	−14	358	380	6
100 gm. coconut oil	12–20°	8	53	61	−15	319	385	20
40 gm. trilaurin	12	0	24	24	0	–	–	–

Stypven Time: To 0.1 ml. of platelet-poor plasma diluted 1 in 4 with saline, is added 0.1 ml. Stypven (Russell viper venom) 1:100,000 and finally 0.1 ml. of $CaCl_2$ *M*. The time recorded is the average of two determinations. Different proportions used for butter and trilaurin and triolein[40].

% Difference: The difference between the fasting and the lipemic measurement is expressed as a percentage of the fasting figure. A minus figure indicates a lengthening.

*Range of chain length of major component fatty acids.

†Abstracted from O'Brien 1956 d.

"meals" of 120 gm. of fat emulsified in skimmed milk, while the control carbohydrate meal was isocaloric and contained 200 ml. of skimmed milk. They gave sardine oil with an iodine value of 185, corn oil, also highly unsaturated, butter and hydrogenated coconut oil (I.V. 2.5). They reported a definite shortening of the silicone clotting time after all the fat meals, the sardine oil not being quite so effective as the other oils. Merskey[40] found no difference in the degree of change in the Stypven time after meals of fat of different degrees of saturation. Thus, it appears that the nature of many oils and the average iodine value do not materially affect the results.

O'Brien[46] gave 50 gm. of various fats to varying small numbers of males and females, aged 20 to 40 years, and records the maximum change in the Stypven time and the changes in the total ether extractable fatty acid (Table 1). With one exception, these results are similar to those obtained with butter (I.V. 30), and support the conclusion that the degree of saturation does not affect the results. In contrast to Keys, however, who reported a shortening of the silicone clotting time after eating coconut oil, this table shows that eating coconut oil and trilaurin does not alter or even lengthens the Stypven time. There is no reason to suppose these fats were not absorbed, but they appear to be absorbed in a different manner since the plasma total fatty acid levels are lower than after the same dose of another fat. To account for the discrepancy between Keys and O'Brien, it is conceivable that after eating coconut oil there is present in the blood a substance that produces a shortening of the silicone clotting time but no change in the Stypven time. No such substance has yet been studied.

TABLE 2.—DISAGREEMENT BETWEEN STYPVEN TIME AND CLOTTING TIME IN GLASS

0.1 ml.	*Clotting Time in Minutes*	*Stypven Time in Seconds*
Platelet-poor Plasma + Saline	5	20
Platelet-poor Plasma + Beef Heart Lecithin	5	8
Platelet-poor Plasma + Platelets a strong suspension, shaken	1	5

Clotting Time: Three tubes containing the mixture indicated were recalcified and the clotting times were averaged.

Stypven Time: To the mixture was added 0.1 ml. of Stypven 1:10,000 and then $CaCl_2$. The figure recorded is the average of two determinations.

It had been assumed by O'Brien[44] that the invariable association of the shortening of the silicone clotting time of whole blood and the shortening of the Stypven time of platelet-poor plasma implied that the two phenomena were caused by the same substance. O'Brien[46a], however, finds that the addition of one volume of 1 mg./ml. beef heart lecithin which contains perhaps 60% plasmalogen (Rapport and Alonzo[57]) to one volume of citrated platelet-poor fasting plasma produces a marked shortening of the Stypven time, but has little or no effect on the clotting time of the plasma in glass

(Table 2). It can, therefore, no longer be assumed that shortening of the clotting time and of the Stypven time are always associated phenomena and are necessarily dependent on the same alteration in the plasma.

O'Brien[46], following up his observation that eggs had a disproportionate activity in shortening the postprandial Stypven time, has given to humans "meals" of carbohydrate and added pure lecithin and a mixture of phospholipids. He finds approximately the same shortening of the Stypven time occurred after eating 10 to 20 gm. of phospholipid as after eating 50 gm. of tri-glyceride. Fifteen grams of triglyceride usually produce minimal postprandial clotting changes, but 2.5 gm. to 5 gm. of phospholipid produce definite changes. He concludes that ingested phospholipid is about five times as active as tri-glyceride in producing clotting changes measured in the presence of Russell viper venom. The effect of ingested phosphoplipid on the postprandial plasma is independent of the effect of the phospholipid added artificially to plasma. Thus, lecithin is inactive in the test tube, but produces marked postprandial changes when eaten.

BIOCHEMICAL. Some of the reported biochemical changes following a fatty meal will now be summarized. Gordon and Cherkes[27] have reported that a meal of 100 gm. of mixed fats produces a rise in the unesterified fatty acids from a fasting level of about 0.5 mEq./L. at the fourth hour; the unesterified fatty acids also increased, but to a lesser degree, during a similar period of starvation, but decreased following a carbohydrate meal. These observations have been confirmed in dogs by Spitzer and Miller[61]. Thus, it would seem that any coagulation phenomena that remain the same during starvation and following a carbohydrate meal cannot be due to changes in unesterified fatty acids. On the other hand, Robinson *et al.*[58] have confirmed the rise in free fatty acids after a fatty meal and Poole[52] has shown that similar quantities of fatty acids added artificially to fasting plasma produced shortening of the Stypven time: O'Brien[46a] confirms this but finds that fatty acids do not greatly shorten the clotting time of plasma. The possibility remains that unesterified fatty acids might be at least partly responsible for some of the observed clotting changes.

Man and Gildea[39] gave a meal of 3.4 gm. of fat per kilogram and recorded an increase in serum total fatty acid of 34% to 133% with an average increase of 62% above the fasting level. The phospholipid increased from 5% to 28% with an average of 8%. Wilmot[70] gave 2 gm. per kilogram of various fats as a "fat tolerance test" after the volunteer had been on a low (30 gm. per day) or a high (150 gm. per day) fat diet. She found a considerably greater response to these meals after the high fat diet. In general, her results are of the same order as those of Man and Gildea. The cholesterol figures show no constant change after these meals. She found that the degree of saturation of the test fat did not influence the results. Morrison, Berlin and Gonzalez[42] also reported that there was an increase in the lipid constituents of plasma after a fatty meal, and that this lipid increase was greater in a group of patients that had had coronary thrombosis than in his controls.

Bloom, Chaikoff and Reinhardt[9] in America and Blomstrand[7] and Borgstrom[12] and their co-workers at Lund, have developed beautiful techniques for following the absorption pattern in rats and cats following the ingestion of lipids labelled with C^{14} and P^{32}. The Lund group found that the long chain fatty acids, whether given as free acids

or tri-glycerides, are absorbed mainly via the lymph and that they are all transported almost entirely as esters, with 2% to 4% transported as phospholipid. The degree of saturation of the ingested fatty acid does not affect the method of transport. Chain length, however, is determinative. The suggestion that short chain fatty acids were transported via the portal vein was put forward in 1946 by Frazer[23] as part of his Partition Theory; and the Lund group showed that the short chain acid, decanoic acid, when ingested, is transported mainly (about 80%) via the portal vein, mostly (68%) in the form of free fatty acid, with 24% as phospholipid and only 7% neutral fat. Of the 20% of the decanoic acid ingested that was transported in the lymph, about 98% was neutral fat and only 2% was phospholipid.

Artom and Swanson[2] showed that in rats some ingested phospholipid can apparently be absorbed intact. Using biosynthesized phospholipids containing radioactive fatty acids, Bloom *et al.*[10] and Blomstrand[8] investigated the effect in rats of ingesting phospholipids. They were able to recover about 60% of the ingested radioactive fatty acid in the lymph, and of this about 80% was in the form of tri-glycerides and 20% as phospholipids. There was evidence that during absorption, extensive hydrolysis of the phospholipids takes place, but that complete hydrolysis does not necessarily occur and that there is considerable randomization of the resynthesized products in the lymph.

There have been several studies of the long-term effect of different dietary fats on the fasting lipid levels. These experiments all show that it takes as much as a fortnight or more to become "adapted" to a change in diet. Ahrends, Blankenhorn and Tsaltas[1] compared the effect of giving animal fat which is largely saturated with that of giving fat of plant origin, including corn oil, peanut butter, and others. These also are mixtures of tri-glycerides, but contain many highly unsaturated fatty acids. In contrast to the immediate postprandial rise in neutral fat and the slight rise in phospholipid and the absence of change in the cholesterol values after such meals, they report that after adaption to a diet of animal fat, the fasting values for cholesterol and phospholipid, but not for neutral fat, were increased. When vegetable fat was substituted, the plasma level of these substances decreased again. Malmros and Wigand[38] and Kinsell and Michaels[34] also showed that the degree of saturation of fat ingested over a period has a marked effect on the plasma lipid levels. Bronte-Stewart *et al.*[14] showed that on a diet of fairly saturated fats, the fasting serum cholesterol and β lipoprotein level is raised and that this change is reversed if unsaturated fats are substituted in the diet. The degree of saturation of the ingested fatty acids thus apparently has no effect on the postprandial absorption but will influence the long-term biosynthesis of the plasma constituents.

The response of an animal to a single fatty meal may be affected by the meal itself and by the state of the animal including its previous dietary habits. If the "meal" is physiological, that is, such as the animal normally eats, then the results are clearly directly applicable to the effect of diet on this animal. If the meal is grossly unphysiological, then the results may not be of general significance. For example, what man eats 120 gm. of fat homogenized in skimmed milk (Keys *et al.*[33]) or 50 gm. of cod liver oil (O'Brien[46]) for breakfast!

The previous dietary habits of the animal may also have a considerable

effect on the results of a single meal, particularly if the preceding diet is unphysiological. Fat transport is probably largely dependent on the intrinsic lipid pattern in the plasma: and the biosythesis of lipids is dependent on the preceding diet. Thus, any change in the diet involves a period of adjustment and equilibration. The length of the period of adjustment depends on the individual animal and the magnitude of the change in the diet. Some experimental diets may be so unphysiological also change in their response to a fatty meal. One volunteer, who ate a normal full diet throughout the period of observation, was given 9 breakfasts containing 50 gm. of fat or 100 gm. of fat. There is collateral evidence that the fats, A, B, and C, were all likely to give the same degree of response, so the results would probably have been similar had the same fat been given on these occasions. This experiment was not designed to test this hypothesis, but it is clear that the metabolic pat-

TABLE 3.—THE DEVELOPMENT BY ONE VOLUNTEER OF "TOLERANCE" TO MEALS CONTAINING 50 gm. FAT

		Stypven Time in Seconds			*Total Fatty Acid in mg./100 ml. Plasma*		
Date	*Fat Eaten*	*Fasting*	*Lipemic*	*Difference*	*Fasting*	*Lipemic*	*Difference*
24–6–56	A	53	35	18	327	474	147
26–6–56	B	48	34	14	305	476	171
29–6–56	C	53	24	29	432	551	119
17–7–56	A	57	33	24	437	514	77
18–7–56	C	51	46	5	416	459	43
10–8–56	A	56	52	4	410	446	36

Stypven Time: As in Table 1.

Difference: The difference in seconds or milligrams between the fasting and the lipemic samples.

that it takes a long time to reach a state of equilibration, or it may never be achieved in a physiological manner.

Several workers, including Wilmot[70] and Ahrends, Blankenhorn and Tsaltas[1] have stressed that it may take several weeks for a human to become "adjusted" to a given diet. Alternatively, if repeated fatty test meals are given which differ from the normal diet, the previous test meals may produce changes in the plasma which will influence the response to subsequent test meals. The phenomenon might show itself as the appearance of "toleration" to the test meal. Swank[63] reported that his dogs rapidly learn to tolerate large fat meals. O'Brien[46] has shown (Table 3) that humans may tern of his volunteer changed during this period, presumably as a result of these 9 meals, since there was no other obvious change in this man. Other volunteers, however, did not develop this "toleration."

The great degree of individual variation in all studies involving fats has not always been adequately stressed in the literature. Given constant conditions, each individual has, but within wide limits, a characteristic fasting clotting time and fasting total fatty acid level, and his response to the same fatty meals is roughly reproducible, unless, or until, he becomes "adapted" to the meal. But the variation between individuals, both as to their fasting levels and to their response to a stand-

ard meal, is enormous. For example, O'Brien[46] gave 50 gm. of fat and found that among 8 volunteers chosen at random, one volunteer repeatedly showed no significant postprandial change in the Stypven time or in the total fatty plasma acids, while the Stypven time of another volunteer decreased by 39% and his total plasma fatty acid increased by 43%. The degree of variation between individuals, both in the fasting plasma fatty acid level and in the response to a fatty meal is evident in Table 1 of O'Brien's first paper[44]. The fasting total plasma fatty acid level ranged from 206 mg. per 100 ml. to 495 among 20 adults aged 20 to 51 years of both sexes. This range and variation is certainly greater than that of many other plasma constituents. It is not known whether a high fasting total plasma fatty acid is of significance, but clearly, it, or some concomitant change, might be. Morrison, Berlin and Gonzalez[42] and Barritt[5] found that on an average the level of fasting plasma lipids was higher in a group of patients who had had myocardial infarction than in a control group of the same age, but there was much overlap between the two groups; and Gofman *et al.*[26] has studied the β lipoproteins in the ultra-centrifuge and has suggested that there is an abnormal increase in the Sf 10–20 class in cases of coronary thrombosis.

PHYSICAL CHANGES. Cullen and Swank[18] reported that in hamsters following a very large fat meal there is an increased adhesiveness and aggregation of red cells. Swank[62,63] reported an increase in dogs' plasma viscosity and a decrease in the sedimentation rate which was accompanied by a fall in the number of circulating white blood cells and platelets and fibrinogen. He was using large doses of fat in dogs and hamsters and, therefore, it is dangerous to assume that these phenomena occur under physiological conditions in man.

The degree of opacity of the plasma or serum is a very rough measure of the number of large chylomicra in the plasma. Keys *et al.*[33] found that after a meal of 120 gm. of fat there was marked opacity in the plasma when the fat was butter fat or corn oil. After fish oil, a less consistent result was obtained and no change occurred after eating 120 gm. of coconut oil. Barritt[5] gave a meal of 60 gm. of butterfat and found that the opacity was greater and persisted longer in patients who had had a myocardial infarction than in the control group, but there was a wide range and considerable overlap between the two groups.

Discussion. COAGULATION. How can the postprandial chemical changes be related to the changes in the clotting tests? It has already been suggested that the rise in free fatty acids plays no major part in causing the clotting changes, but the possibility cannot be excluded.

O'Brien[44] has shown that there is no correlation between the increase after a fatty meal in total ether extractable fatty acid, which would have been mostly tri-glycerides, and the clotting time, suggesting that the tri-glycerides are not responsible for the observed changes. This conclusion is supported by the observation of Poole[54] and confirmed by O'Brien[46b] that physiological quantities of tri-glycerides introduced into platelet-poor plasma have no effect on blood coagulation.

The other class of lipids known to increase slightly after a fatty meal is the phospholipids. Phospholipids, with their two polar charges, soluble in fats, in fat solvents and dispersable in water, but insoluble in it, are a most remarkable group of substances. For example, the physical properties of a mixture of two phospholipids may be quite dif-

ferent from that expected from the behavior of each examined separately. Wadsworth, Maltaner and Maltaner[65] showed that various clotting and precipitation tests were extremely sensitive to the concentration of protein, phospholipid and calcium, and, that slight alteration might change enhanced activity into inhibition. Rapport[56] showed that phosphatidyl-serine alone was only moderately active in a clotting system, and this activity was greatly increased by the addition of two volumes of lecithin which alone was inactive. He also reported that one volume and five volumes of lecithin were less active than two volumes and suggested that this indicates a specific lipid-lipid interaction, and that lecithin is not acting merely by increasing the dispersion of the phosphatidyl-serine by mixed micelle formation. The dispersion of phospholipids in water has been studied by Holtfreter[32], some of whose drawings of myelin bodies look very like the crenated forms of platelets and Golgi organs. They are probably present in all cell membranes where their orientation in the very large molecules such as the β lipoproteins is likely to be altered by minute changes in pH, salt concentration and might easily be altered by the surface changes involved in "contact."

The phospholipids play an essential part in blood coagulation. Bordet's "cytozyme"[11] present in platelets and crude lecithin was certainly active by virtue of its phospholipid content. Plasma Thromboplastin Component (P.T.C. or Christmas factor) which probably takes part in the earliest phases of *in vitro* blood coagulation associated with "contact" may be a β lipoprotein which contains a phospholipid moiety. O'Brien[47] has shown that procedures likely to destroy phospholipid, inactivate the Christmas factor in normal plasma. O'Brien[45] has shown that platelets are active in many clotting systems by virtue of their content of a substance very like phosphatidyl-ethanolamine; and Wallach, Surgenor and Walters[68] have shown that the chromatographic pattern of a platelet extract has a spot in the same place of a phosphatidyl-ethanolamine marker. The lipid component of platelets may form part of intrinsic thromboplastin complex; but if this is so, the phospholipid is in a changed state, since it is no longer inactivated by cobra venom and bee venom enzyme systems that inactivate platelets and Christmas factor (O'Brien[47]).

A number of phospholipids have already been shown to be active in the various clotting systems (O'Brien[46a]). Egg phosphatidyl-ethanolamine (P.E.), saturated and unsaturated, are both active, the difference in activity possibly being explained by differences in the degree of dispersion (O'Brien[45]). The brain P.E. tested was probably less "pure" (thus, possibly containing an active "impurity"); but was better dispersed and more active than the egg P.E. Maclagan and Billimoria[37] have now shown that a fraction prepared from butter containing P.E. and galactose was very active, but its final composition is not clear. Rapport[56] has shown that phosphatidyl-serine is also active under some conditions. O'Brien[46a] has shown that diphosphoinositide (Hawthrone[31]) was maximally active. It will be noted that all these substances have a net negative charge and thus differ from the inactive compounds, lecithin and sphingomyelin which carry no net charge. Thus, it is likely that there are a whole group of substances with a basic resemblance to phosphatidyl-ethanolamine, which, if present in the blood singly or together, would all produce effects similar to those of platelets.

O'Brien[44] has shown that *in vivo*

most of the "total plasma phospholipid" as estimated chemically, is inactive in the Stypven time system and is presumably bound in the lipoprotein molecules. After extraction from the protein molecule, the phospholipid can be shown to become active[46b]. Chargaff[16] has studied the composition and shape of a protein isolated from brain that had great thromboplastic activity; this is presumably the active agent in the brain extract used in the normal one-stage Quick clotting time.

The extreme sensitiveness of the Stypven time to the presence of minute traces of P.E. added to the plasma has already been mentioned. It has also been shown (O'Brien[46]) that, provided the plasma has been carefully collected, fresh platelet-rich plasma has the same Stypven time as plasma from which most of the platelets have been removed. If the platelets are broken up by violent agitation, then the Stypven time is markedly shortened. This shortening is presumably due to the liberation of the phosphatidyl-ethanolamine-like phospholipid from the platelets. These experiments show that the phospholipid or other accelerating substance in intact platelets is not immediately "available," at least under the artificial conditions of this test. It seems likely that the intact normal platelet is in some respects inactive, and it is only after the initiation of blood coagulation (possibly by Christmas factor, which contains phospholipid) that platelet viscous metamorphosis occurs and the activated granules of Bergsagel[6] are available to play their part; these granules are probably active by virtue of their phospholipid content.

It is possible, but quite unproved that a small amount of "available" active phospholipid might have a great and disproportionate importance in blood coagulation *in vivo*. Being already active, it is independent of any stimulus such as contact which starts the normal chain reaction leading finally to the liberation of phospholipid from platelets. On the other hand, since the Russell viper venom accelerated clotting time is a completely artificial system, it is possible that the phospholipid which acts as a powerful accelerator is simply a co-factor to the venom. This hypothesis is unlikely, since all of the phospholipids tested so far, except beef heart lecithin (O'Brien[46a]), which accelerate the Stypven time, also can replace platelets in the thrombin generation and other tests less artificial than the Stypven clotting test.

The Lund group of workers have shown that when tri-glyceride is fed to rats and cats most of it is transported via the lymph. Of this lymph fat, 98% is tri-glyceride and 2% phospholipid. If phospholipid is fed, then 80% of the absorbed fatty acid in the lymph is tri-glyceride, but 20% is phospholipid. Thus, the plasma phospholipid level after a phospholipid meal might be ten times higher (2% to 20%) than after a tri-glyceride meal. O'Brien[46] has reported that phospholipids fed to humans appear to be about five times as active in producing acceleration of the Stypven time postprandially as tri-glycerides. This observation is in good agreement with that of the Lund workers, if, in fact, O'Brien's Stypven times are measuring free plasma phospholipid. The randomization occurring in the resynthesized phospholipids reported from Lund would also explain why the lecithin, inactive when artificially introduced into the Stypven clotting system produced postprandial changes when eaten.

The other basic observation of the Lund group, that decanoic acid is absorbed largely via the portal vein

(while the longer chain fatty acids are absorbed via the lymph), may well be related to the observation of O'Brien[46] that the ingestion of trilaurin and coconut oil do not produce the same clotting changes as the ingestion of the longer chain fatty acids. This observation suggests that in man too, the short chain fatty acids are metabolized quite differently from the longer chain fatty acids.

To summarize, the concentration of free fatty acids, tri-glycerides and phospholipids increase in the plasma after a fatty meal. Tri-glycerides are almost certainly not the cause of the postprandial changes in coagulation found in platelet-poor plasma *in vitro*, although they may be precursors of fatty acids, as, for example, in the heparin clearing factor system. Free fatty acids might be responsible, but it is suggested that the phospholipids play a major part. The presence of even small quantities of "available" phospholipid in the blood stream postprandially, may be of importance in clot formation *in vivo*, since platelets (active in *in vitro* coagulation systems by virtue of their phospholipid content) may be inactive *in vivo* until the phospholipid in them is released.

Evidence has been presented which suggests that the ingestion of phospholipid leads to a high level of free available phospholipid in the blood. Ingested short chain tri-glycerides seem to be metabolized differently and do not appear to liberate available phospholipid during absorption.

FIBRINOLYSIS. It is often tacitly assumed that this highly unstable fluid, blood, always stays liquid in the body unless a gross thrombosis indicates the contrary. So, the clotting factors and their inhibitors have been studied extensively. It was suggested by Nolf[43] in 1908, and there is some evidence (Crawford and Levine[17], and Duguid[20]) to show that blood is clotting all the time in the body. If this were so, then the system whereby the unwanted fibrin was removed would assume extreme importance. Fibrinolysis has received far less study than blood coagulation, but the subject is reviewed by Astrup[3,4]. He emphasizes the scarcity or absence of blood vessels supplying the media and subintima of the large arteries and thinks that the nutrition of this area must be provided by diffusion of nutrients from blood in the lumen. Fibrin deposited on the vessel wall, if not rapidly lysed, would then, not only be covered by endothelium as Duguid[19] suggested, but also would act as a barrier to the diffusion of nutrients and cause necrosis.

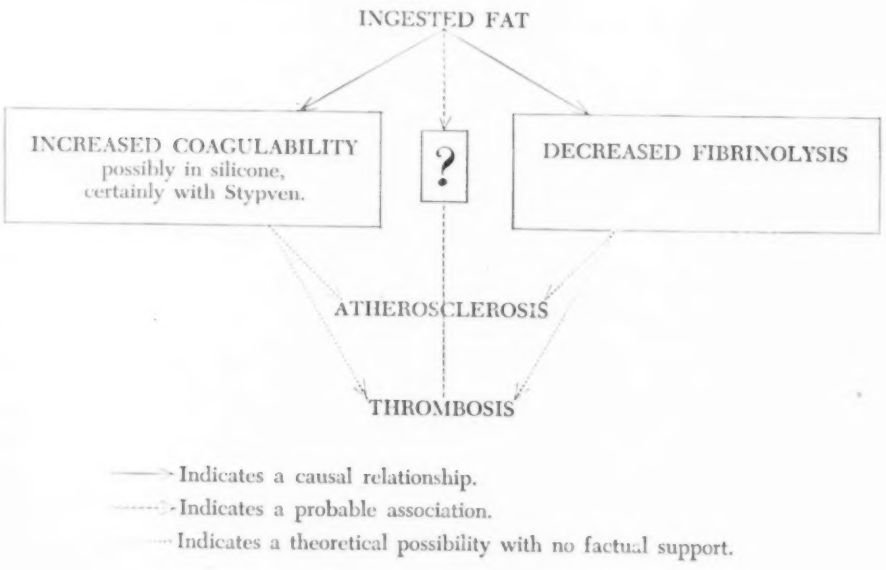
Greig[29] has made the most interesting observation that the normal fibrinolytic activity of the blood is markedly decreased by the presence of lipemia; furthermore, he has shown that, after eating saturated fats, this effect is more marked than that after eating unsaturated fats.

If this work is confirmed, it fits in remarkably well with the totally different experiments of Ahrends, Blankenhorn and Tsaltas[1] and others who have shown that eating saturated fats for a long period raised the fasting plasma level of cholesterol and of the β lipoproteins, while unsaturated fats had no effect. It has already been mentioned that this protein is thought to be related in some way to the incidence of coronary vascular disease.

OTHER SYSTEMS. This review has considered the coagulation system and the fibrinolytic system as if they were independent. There is fragmentary evidence which might suggest that these two systems, coagulation and fibrinolytic, and also the heparin clearing factor system and the complement system are all interrelated. For ex-

ample, the following substances are anti-complementary: thrombin, phosphatidyl-ethanolamine, thromboplastin and Russell viper venom (Pillimer[50]). The ingestion of fat inhibits fibrinolysis (Greig[29]) and accelerates some clotting tests. Heparin, an anticoagulant, is related to the naturally occurring heparin clearing factor and affects the flotation pattern of the β lipoproteins (Graham *et al.*[28]), although there is some evidence that the mechanisms involved may differ (Spitzer[60]). Choline deficiency may produce atheroma and myocardial hemorrhages in rats, while feeding beef fat may make these lesions worse (Wilgram, Hartroft and Best[69]). The synthetic ester, p-toluene sulphonyl L-argenine methyl ester is hydrolyzed by the activated first part of Complement (C^1), by plasmin (fibrinolysin), by thrombin and by trypsin (Lepow *et al.*[35]).

Even if it were possible, this is not the place to attempt an integration of these diverse phenomena. They are mentioned to emphasize the probability that at least these four systems are interrelated, and that the phospholipids and lipoproteins will be found to play a vital part in each. This emphasizes the importance of further study of each system, and that phenomena relevant to the other systems are likely to emerge. The ubiquitous and enigmatic phospholipids are common ground and they are also certainly involved in the problems of atherosclerosis.



Conclusion. It is reasonably well established that there is some connection between the long-term fat consumption of a community and the incidence of atherosclerosis, although there are many other etiological factors. Some saturated fats eaten over a long period produce an elevation of some plasma lipids, while other unsaturated fats do not. After a single fatty meal there are changes in the biochemical and physical properties of the blood. There

are changes in some *in vitro* coagulation tests, in the fibrinolytic and in the heparin clearing factor systems. Which, if any, of these changes is relevant to the effect of ingested fat on atherosclerosis is quite unknown.

The present position might be summarized by the diagram on page 387.

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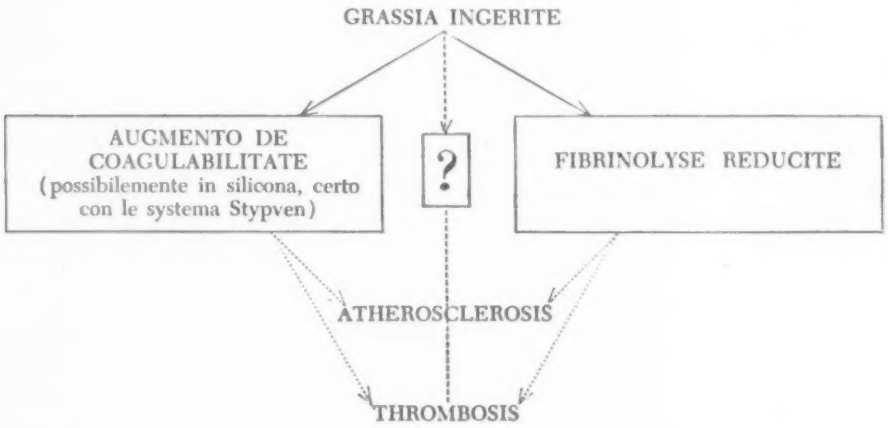
SUMMARIO IN INTERLINGUA

Ingestion de Grassia, Coagulation Sanguinee, e Atherosclerosis

Es establite satis firmemente que il existe un connexion inter le consumption de grassia a longe vista in un communitate specific e le incidentia de atherosclerosis, ben que multe altere factores etiologic es etiam implicate in le situation. Certe grassias saturate, ingerite durante longe periodos de tempore, effectua un elevation del concentration de certe lipidos del plasma. Certe altere grassias, del typo non-saturate, non exerce iste effecto. Post un sol repasto grasse, alterationes occurre in le qualitates biochimic e physic del sanguine. Il ha alterationes in certe tests de coagulation in vitro in le systemas del factores fibrinolytic e

del factores de clearing de heparina. Le quales de iste alterationes es possibilemente significative con respecto al effecto de grassias ingerite super le disveloppamento de atherosclerosis es completemente incognoscite.

Nostre conception al tempore presente pote esser summarisate in le sequente diagramma:



——> Indica un relation causal.

·····> Indica un association probabile.

····· Indica un possibilitate theoric sin supporto concrete.

SUMMARIO IN INTERLINGUA

(See page 391 for original article)

Test del Tolerantia a Calcium-Digitalis
Reporto Clinic del Prime 24 Essayos

1. Es discutite le principios (e le mesuras precautionari) del test del tolerantia a calcium-digitalis.

2. Le technica del test del tolerantia a calcium-digitalis es describite in detalio.

3. Le test esseva executate 24 vices in 15 subjectos human in stato de disfallimento congestive. Le resultatos es summarisate in tabula 4. Sex patientes additional in stato de disfallimento congestive esseva testate in 8 interprisas de controlo. Le resultatos de istos es summarisate in tabula 3. Occurreva nulle complicationes e nulle mortes in o le gruppo experimental o le gruppo de controlo.

4. Le interpretation del datos del tests e le computation del dosage complemental de digitalis per medio de un formula constante es demonstrate.

5. Es explicate le correcte uso de Na_2EDTA (dinatrium-ethylenediamino tetraacetate) como agente de chelation de calcium in reverter persistente o emergente punctos terminal del electrocardiogramma.

6. Es listate indicationes e contraindicationes pro le test super le base del presente nivello de nostre experientia.

CALCIUM-DIGITALIS TOLERANCE TEST
A CLINICAL REPORT OF THE FIRST 24 TRIALS*

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In previous publications[7,8] the literature and the experimental work supporting the Calcium-Digitalis Tolerance Test has been discussed. This test is based upon the inverse, quantitative and synergistic relationship between calcium and digitalis with the production of EKG endpoints (that is, digitalis toxicity). The patient is given increasing increments of 10% $CaCl_2$ intravenously at regular intervals until the EKG endpoint, usually transient, is provoked. Should the EKG endpoint persist, it can be reversed in one minute or less by giving an appropriate quantity of the calcium chelating agent, Na_2EDTA. The more digitalized a patient is and the greater the myocardial sensitivity to digitalis, the less calcium is required to produce an EKG endpoint and *vice versa*. It is, therefore, possible to determine the degree of digitalization in terms of total tolerance for digitalis measured to the point of toxicity. In the absence of history, it will be possible to detect the presence of digitalis. Once the level of existing digitalization has been determined a complemental dose of digitalis can be calculated and administered. Thus, nontoxic, safe, maximum levels of desired digitalization can be achieved.

It should be emphasized that the safety of this test depends upon two factors both of which reverse the induced hypercalcemia to interrupt the synergism between calcium and digitalis. One factor is the use of Na_2EDTA.† This drug immediately renders the chelated calcium physiology unavailable. The other factor is the normal serum calcium clearance rate as determined by Bronner *et al.*[2]. It is our opinion that the effect of the serum calcium clearance rate is primarily responsible for the transient EKG endpoints observed in the course of the test trials. There is good evidence (Bronner and Harris[1], Hansard, Comar and Davis[3], and Thomas *et al.*[9]) that the rate of serum calcium clearance is in part an inverse function of age.

The test dosage schedule presented here has proven satisfactory for adults. Additional experience with this test

*Supported by the Spaulding Fund of Harper Hospital.

†Na_2EDTA (Disodium ethylenediamine tetraacetate) is prepared in pharmaceutical quality and was generously supplied by Riker Laboratories, Los Angeles, California.

may indicate that some minor modification of the test dosage schedule of 10% $CaCl_2$ may be required for the geriatric age group (see Controls and Case 6, Table 3).

Method. The performance of the test is listed step by step:

1. Properly identified syringes containing the several doses of $CaCl_2$ in Table 1 and 10.8 ml. of 10% Na_2EDTA are prepared.
2. A baseline EKG is taken.
3. Through a procaine wheal in the skin a #15 needle is passed into a vein of the forearm or hand.
4. By aseptic technique a #22 polyethylene tube is threaded through the lumen of the needle into the vein a distance of about 15 cm.
5. A 3-way stopcock is affixed to the distal end of the polyethylene tubing and 5% glucose in water is started to keep the tubing patent between injections.
6. A sweep second hand watch is started and $CaCl_2$ is administered exactly according to the schedule in Table 1. A continuous EKG or oscillographic recording is observed for endpoints.
7. When either an EKG endpoint or the entire test dose schedule has been administered, whichever occurs first, the test is terminated.
8. If the EKG endpoint persists or becomes emergent, 10% Na_2EDTA from the previously prepared syringe is administered through the stopcock and tubing according to dosage in Table 2.

Results. The Calcium-Digitalis Tolerance Test has been performed 24 times in 15 human beings in congestive failure without complication or mortality.* A control series of 8 additional trials in 6 nondigitalized patients in congestive failure was also performed without morbidity or mortality.

Controls. It was originally planned that each patient would serve as his own control. That is, each nondigitalized patient in congestive failure would receive the full test dose schedule of $CaCl_2$. Following partial or full digitalization, the test was to be repeated and the calculated complemental dose administered. This was not possible in almost all of the cases due to factors beyond our control.

TABLE 1.—TEST DOSAGE SCHEDULE OF 10% $CaCl_2$*

Exactly at Time	*Begin Test Dose Number*	*Ml. of 10% $CaCl_2$ per Each Dose*
0 min.	1	.5 ml.
2.5	2	1.0
5.0	3	1.5
7.5	4	2.0
10.0	5	3.0
12.5	6	4.0
15.0	7	5.0
17.5	8	6.0
20.0	9	7.0

*All test doses are given in sequence strictly according to time. Each and every test dose, regardless of volume, is delivered at an even rate over a period of 30 seconds exactly. $CaCl_2$ is used in the test dose schedule for human beings rather than calcium gluconate as was done in dogs[7,8] because 10% $CaCl_2$ contains 3 times as much calcium/ml. (27 mg.) as does 10% calcium gluconate (9 mg.).

Six patients in congestive failure in the nondigitalized state received 8 full test dose schedules of $CaCl_2$ (Table 3). No false endpoints developed in 6 control tests in 4 patients within the test dose range. A false endpoint here is defined as an EKG change of digitalis toxicity due to calcium in the absence of digitalis. It will be recalled that if

*Another investigator elsewhere using this test in an independent series of patients encountered one death in an elderly patient who had had two myocardial infarcts and arteriosclerotic heart disease with angina pectoris. The test was continued intentionally two test doses beyond the true endpoint. The patient developed ventricular tachycardia that was successfully reversed to normal sinus rate and rhythm within 20 seconds with Na_2EDTA. The patient died shortly afterwards and the findings at necropsy disclosed a 3rd myocardial infarct of about 10 days' duration.

sufficient calcium is given rapidly EKG changes of digitalis toxicity can be produced in the nondigitalized, experimental animal. In two controls (L.P. and M.K.) false endpoints were obtained within the test dose range. However, EKG changes of coronary insufficiency were obtained on exercise in patient L.P. (See "Remarks," Table 3.) The second control, M.K., to exhibit a false endpoint was the oldest patient in either the trial or control group, being 79 years of age. This elderly patient may reflect the slower rate of serum calcium clearance in elderly patients (paragraph 2). Therefore, the test schedule of $CaCl_2$ presented here appears to be satisfactory for use in adults in congestive failure. However, more extensive clinical trials of the test dose schedule with controls will be required to establish its validity with certainty.

TABLE 2.—DOSAGE SCHEDULE OF 10% Na_2EDTA*

If the EKP Endpoint Persists After		*Then Give Over a Period of One Minute*
Test Dose Number	*Ml. of 10% $CaCl_2$ per Test Dose*	*10% Na_2EDTA as Follows: Ml. of 10% Na_2EDTA*
1	.5	.75
2	1.0	1.50
3	1.5	2.30
4	2.0	3.00
5	3.0	4.50
6	4.0	6.00
7	5.0	7.60
8	6.0	9.30
9	7.0	10.80

*If, for example, during the test an endpoint which persists for more than one minute or is emergent after a particular test dose of calcium chloride is administered, the corresponding dose of 10% Na_2EDTA is given. At least one minute should be taken for the administration of such a dose. This dose of 10% Na_2EDTA will chelate about ½ the calcium content of the provoking dose of calcium chloride. This is sufficient to break off the synergism between calcium and digitalis supporting the toxic EKG endpoint.

RESULTS OF CLINICAL TESTS. Table 4 summarizes the experience with 24 trials of this test in 15 patients in congestive failure in a variety of clinical situations. No complications and no mortality were encountered in this series.

Discussion. LEVELS OF DIGITALIZATION. In a preceding paper[7] we were able to prove levels of digitalization by an adaptation of the work of Hatcher[4]. To apply the same method of proof in human beings would place each patient in jeopardy at least three times. Since this was unconscionable, the determination of the levels of digitalization was established less exactly by an alternate method. This was accomplished in part by extrapolation of the experimental work and in part by empirical methods. It was eventually learned that a positive response at a particular test dose of $CaCl_2$ could be correlated with a corresponding level of digitalization expressed as a percentage of the total tolerance measured to the point of toxicity (see Fig. 1).

CALCULATION OF THE COMPLEMENTAL DOSE. Figure 1 indicates that if a digitalized patient reacts with an EKG endpoint, for example, after a 6 ml. test dose of $CaCl_2$ he is digitalized to a level of 50% of toxicity. In other words, the digitalizing dose can be expressed as a per cent of the toxic dose. Algebraically:

Where

x_1 = % of toxicity from test data expressed in decimal value

t = toxic dose of digitalis in milligrams

D = original "digitalizing" dose in milligrams

TABLE 3.—SUMMARY OF CONTROLS*

Patient, Age, Sex, Diagnosis	*Baseline EKG*	*Largest Dose of $CaCl_2$*	*False EKG Endpoint*	*Remarks*
1. J.B. 70 yrs. Male HHD	AF & LVH	8 ml.	None	Total $CaCl_2$ test schedule given 3 times with identical results at 3-day intervals.
2. D.D. 77 yrs. Male ASHD	AF & occas. PVS	7 ml.	None	
3. A.A. 74 yrs. Male ASHD	LVH	7 ml.	None	See test results on this patient, Table 4.
4. F.G. 70 yrs. Male ASHD	Freq. PAS & inversion of T, Lead III, V_6	8 ml. 8 ml.	None None	Had 1 PVS after 5 ml., 3 single PVS's after 7 ml. and 2 ten-second runs of AF after 8 ml. Single PVS's are *not* endpoints. Baseline EKG and elevated lactic dehydrogenase indicate subclinical myocardial damage.
5. L.P. 44 yrs. Female HHD & ASHD	LVH	5 ml.	2 bouts AF of 6 sec. each in 20-sec. period	History of chest pain "not typical" of angina pectoris. EKG changes of coronary insufficiency produced by exercise. May account for calcium sensitivity in such a young individual.
6. M.K. 79 yrs. Female ASHD	Freq. PAS with defective I-V conduction	6 ml.	AFl alternating with AF for 50 minutes	Oldest patient in either control or test series (see paragraph 2). Two days after test received 0.8 mg. Cedilanid with no toxicity by EKG. Later slowly digitalized with Digitora without toxicity.

Abbreviations:

HHD	Hypertensive heart disease
ASHD	Arteriosclerotic heart disease
AF	Atrial fibrillation
LVH	Left ventricular hypertrophy
PVS	Premature ventricular systoles
PAS	Premature atrial systoles
AFl	Atrial flutter
I–V	Intra-ventricular

* This table summarizes the 8 trials of the entire test dose schedule of 10% $CaCl_2$ in 6 nondigitalized patients in congestive failure. See text for additional discussion.

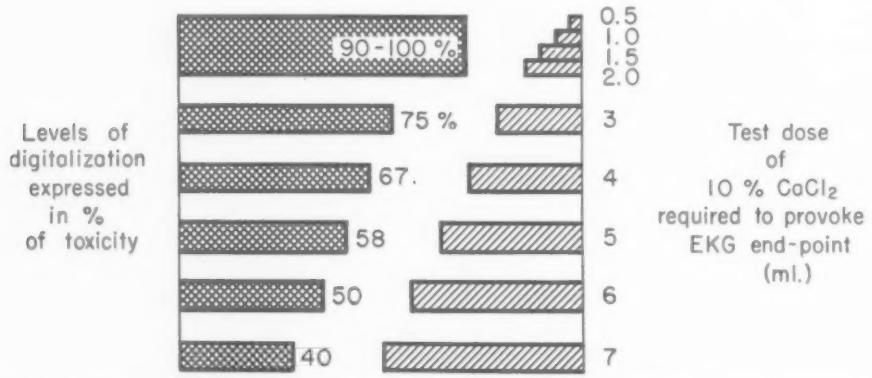

Fig. 1.—Levels of digitalization are expressed as a percentage of total tolerance measured to the point of toxicity. The particular $CaCl_2$ test dose provoking an EKG endpoint correlates with a corresponding level of digitalization.

Endpoints in patients arising from doses of $CaCl_2$ from .5 ml. to 2 ml. indicate from 90% to 100% digitalization and complemental dosage of digitalis should not be contemplated.

The test is constructed to detect levels of digitalization between 40% and 100% of toxicity. These values have proven adequate for this series of trials, but should be considered tentative until confirmed by additional clinical trials.

c = complemental dose in milligrams

(1) $x_1(t) = D$

solving for t

(2) $t = \frac{D}{x_1}$

We see that the toxic dose is equal to the "digitalizing" dose divided by the % of toxicity obtained from the test data. Then the toxic dose, $\frac{D}{x_1}$, less the digitalizing dose must equal the complemental dose. Thus:

(3) $\frac{D}{x_1} - D = c$

or in equivalent algebraic form*

(4) $\frac{D(1 - x_1)}{x_1} = c$

If the calculated complemental dose "c" were administered using the same glycoside as in the original digitalization, the patient would then be digitalized to a level which would be just toxic. It follows that a percentage (80%, 90%) of the calculated complemental dose would render the patient digitalized to maximum levels of tolerance and just short of toxicity. This correction can be achieved by adding a contant, k,† with a value of .80 or .90 to expression *(4)*. The expression then becomes *(5)* $k\left[\frac{D(1-x_1)}{x_1}\right] = c.$

(Actually the value given to k controls the extent to which the complemental dose will approach toxicity such that with k equal to 1 the complemental dose will just cause toxicity.) An illustrative use of equation *(5)* is in order.

EXAMPLE: A patient in congestive failure was given 1.2 mg. of Digitoxin and the Calcium-Digitalis Tolerance Test indicated the digitalizing dose was equal to 75% of his tolerance for the drug. Then in expression (5) D = 1.2 mg., $x_1 = .75$, and k may equal .80 to .90. Substituting and solving:

$$k\left[\frac{D(1-x_1)}{x_1}\right] = c$$

$$.90\left[\frac{(1.2)(1-.75)}{.75}\right] = c$$

$$.90[.4] = c$$

$$.36 \text{ mg.} = c$$

Therefore .4 mg. of Digitoxin given in addition to the "digitalizing dose" would render him just toxic. With k equal to .90 the complemental dose would be a safe, maximal complemental dose of .36 mg. of digitoxin.

Expression *(5)* is useful not only in determining complements of the original digitalizing dose but also it can be used in the determination of the adequacy of the maintenance dose and its correction. Evaluation and correction of the level of digitalization achieved by maintenance dosage is compatible with expression *(5)* provided two testing procedures are used: One test being performed after the original "digitalizing dose" has taken effect and a second test being performed after an interval of time with the patient on maintenance dosage of digitalis. It can be shown that from expression *(5)* a more general equation can be derived,

(6) $k\left[\frac{D(1-x_2)}{x_1}\right] = c$

where x_1 is the % of toxicity obtained from the data of the 1st test and x_2 is the % of toxicity obtained from the data of the 2nd test, both values being expressed in decimals. An illustrative example using expression *(6)* is in order:

EXAMPLE: A patient was treated for congestive heart failure 4 months ago with a "digitalizing dose" of 1.2 mg. of Digitoxin. The Calcium-Digitalis Tolerance Test indicated he was digitalized to a level

*We are indebted to Gerald C. Timmis, M.D., of Harper Hospital for the forms of equations *(4)* and *(6)*.

†For purposes of the computation of the complemental dosage of digitalis early in this series, k was given a value of .6 which was gradually increased to a maximum of .8.

of 75% of his tolerance. This was a therapeutically effective level in his case and complemental dosage was not given. He was put on maintenance dosage of Digitoxin. Because of recurrence of symptoms now, 4 months later, the clinician suspects the maintenance dosage to be inadequate. Without giving additional digitalis, the tolerance test is performed and the present level of digitalization in terms of his total tolerance is now 50%. Then in expression (6) D = 1.2 mg., $x_2 = .50$, $x_1 = .75$, and k again may equal from .80 to .90. Substituting in (6) we have

$$k\left[\frac{D(1-x_2)}{x_1}\right] = c$$

$$.90\left[\frac{(1.2)(1-.50)}{.75}\right] = c$$

$$.90[.8] = c$$

$$.72 \text{ mg.} = c$$

It is evident that .8 mg. of Digitoxin given to this patient would render him just toxic. When corrected by k (.90), the maximum safe complemental dose of Digitoxin is found to be .72 mg.

Thus, with the use of a formula and the Calcium-Digitalis Tolerance Test, it is now possible to determine what the "digitalizing dose" means in terms of a patient's total tolerance for digitalis and to calculate therefrom the maximum, safe complemental dose which can be administered. And, similarly, when inadequate maintenance doses gradually reduce the level of digitalization in a patient, maximum, safe complemental doses can be calculated to restore higher levels.

TABLE 4.—SUMMARY OF CLINICAL TRIALS OF CALCIUM-DIGITALIS TOLERANCE TEST*

Patient, Age, Sex, Diagnosis	*Pre-test Digitalis Therapy*	*Baseline EKG*	*$CaCl_2$ Dose Provoking EKG Endpoint*	*EKG Endpoint*	*Dose of Na_2EDTA*
1. A.M. 65 yrs. Male ASHD	Digitoxin 0.1 mg./day	SA	0.5 ml.	Wandering atrial pacemaker, 25 min. duration	None
2. A.G. 51 yrs. Male HHD	Cedilanid, 1.2 mg. intravenously 2 hr., 45 min. before test	LVH	3.0 ml.	1st degree heart block; two 30-sec. episodes in two minutes.	None
3. W.G. 56 yrs. Male HHD	Cedilanid, .8 mg. intravenously, 2 hr., 45 min. before test	LVH with frequent unifocal PVS.	4.0 ml.	Increased freq. of multifocal PVS.	6 ml.
4. L.M. 51 yrs. Female RhHD	Digitoxin .15 mg./day	Rapid AF with multifocal PVS	1.5 ml.	Increased freq. of multifocal PVS with runs of bigeminy.	2.3 ml.
5. T.R. 70 yrs. Male ASHD	Digitora ?? 1.28 gr. daily??	Rapid AF, LVH occas. multifocal PVS	7.0 ml.	None	None
6. H.N. 48 yrs. Female RhHD	Digitoxin, .2 mg./day; toxic; no Digitoxin 1 wk. before test	Continuous AF	1.0 ml.	Recurrent PVS; duration 2½ min. plus.	None
7. P.R. 51 yrs. Female ASHD, HHD	Digoxin, total of 3 mg. in 3 days	LVH	5.0 ml.	Short runs PVS and 1st degree heart block; for 13 min.	None

Complemental doses in this series have also been calculated for glycosides of higher potency per mg. than the original glycoside used for the digitalization (that is, Cedilanid or Digoxin complementing Digitoxin). In order to calculate complemental doses involving differing glycosides, a common unit is required that precisely interrelates the potencies of the several glycosides. To this end Cat Units were used but due to inherent inaccuracies of such units the doses calculated therefrom were generally smaller than the correct theoretical figure. That is the complemental doses calculated with the use of Cat Units were of a clinically safe order but were less than the maximum, theoretical dose that could be tolerated. With Digoxin, however, satisfactory calculations were obtained using a Cat Unit value of .28 mg.

Na_2EDTA: Na_2EDTA was required to reverse EKG changes of digitalis toxicity provoked by hypercalcemia in this series only 4 times in 24 trials. The remaining endpoints were benign and transient. When Na_2EDTA is used it should be administered in strict accordance with the dosage schedule shown in Table 2. Na_2EDTA combines with the calcium stoichiometrically. The hypercalcemia needs to be lowered only a few milligrams per milliliter of plasma in order to interrupt the synergism with the digitalis and re-

TABLE 4.

Complemental Dose of Digitalis	*Retest Dose $CaCl_2$ Provoking Endpoint*	*Retest EKG Endpoint*	*Dose of Na_2EDTA*	*Remarks*
None	None	None	None	Demonstrated to be fully digitalized.
Cedilanid, 0.4 mg. intravenously, 25 minutes after test.	1.5 ml.	1st. degree heart block; 30-second episodes intermittently for 30 minutes	None	Demonstrates quantitation.
Cedilanid, .25 mg. intravenously, 25 minutes after test.	1.5 ml.	SA with increased frequency of multifocal PVS	None	Demonstrates quantitation.
None	None	None	None	Test performed to determine whether baseline arrhythmia was due to decompensation or to intoxication.
Digoxin, .5 mg./day for 3 days THEN Cedilanid 0.6 mg. intravenously, 2 hr. 30 min. before retest.	None	None	None	Another question of whether arrhythmia was due to decompensation or digitalis intoxication. Became toxic after complemental dose of Cedilanid. Baseline arrhythmia shown to be due to decompensation.
None	None	None	None	Test confirms probability that patient was maximally digitalized at time of test.
Digoxin, Mtn. dose increased from .25 to .75 mg. daily for 10 days then tested.	1.0 ml.	Short runs of PVS & PNS; duration less than 30 seconds.	None	Day after retest patient had nausea and vomiting relieved by reduction of maintenance dose from 0.75 mg. Digoxin to 0.50 mg. Patient demonstrated to be digitalized to borderline of toxicity.

TABLE 4.—SUMMARY OF CLINICAL TRIALS OF CALCIUM-DIGITALIS TOLERANCE TEST*
—(*Continued*)

Patient, Age, Sex, Diagnosis	*Pre-test Digitalis Therapy*	*Baseline EKG*	*$CaCl_2$ Dose Provoking EKG Endpoint*	*EKG Endpoint*	*Dose of Na_2EDTA*
8. O.G. 75 yrs. Male ASHD	Digitoxin, 0.2 mg./day	LBBB, freq. PAS & PVS	1.5 ml.	Multifocal PVS in couples; duration 10 min. before Na_2 EDTA	1.5 ml.
9. L.D. 58 yrs. Female	?? Digitalis ?? type & amount unknown	LVH	6.0 ml.	Diminution in amplitude P waves; duration 1½ minutes.	None
10. J.T. 67 yrs. Male ASHD, Cor pulmonale	Digoxin and Digitoxin in varying dosage	Wandering sinus pacemaker, LVH, with SA & occas. PVS	7.0 ml.	None	None
11. H.K. 65 yrs. Male ASHD, HHD	Cedilanid, 0.8 mg. intravenously, 3 hrs. prior to test	RBBB with occas. PVS	5.0 ml.	Multifocal PVS in pairs; duration two minutes.	None
12. C.L. 64 yrs. Male	Cedilanid, 0.6 mg. intravenously, 3 hrs. prior to test	LVH	7.0 ml.	None	None
13. A.L. 67 yrs. Male HHD	Cedilanid, 0.8 mg. intravenously, 3 hrs. prior to test	LVH with occas. PVS	6.0 ml.	Diminution in amplitude P waves; duration less than 2 min.	None
14. J.S. 63 yrs. Male HHD	Digoxin, 0.5 mg./day	LVH	4.0 ml.	PVS and two PNS in a single run; recurred 2 times in 3½ min.	None
15. A.A. 74 yrs. Male ASHD	Cedilanid, 0.8 mg. intravenously, 3 hrs. prior to test	LVH	7.0 ml.	None	None

Abbreviations: ASHD Arteriosclerotic heart disease; HHD Hypertensive heart disease; RhHD Rheumatic heart disease; SA Sinus arrhythmia; LVH Left ventricular hypertrophy; PVS Premature ventricular systole; AF Atrial fibrillation; LBBB Left bundle branch block; PAS Premature atrial systole; PNS Premature nodal systole; RBBB Right bundle branch block

TABLE 4.—(*Continued*)

Complemental Dose of Digitalis	*Retest Dose $CaCl_2$ Provoking Endpoint*	*Retest EKG Endpoint*	*Dose of Na_2EDTA*	*Remarks*
None	None	None	None	Test indicated patient to be fully digitalized *despite* progressive dyspnea, orthopnea and edema. Therefore treated with mercurial diuretics, salt restriction, bed rest, with maintenance dose digitoxin continued. Completely asymptomatic on this management.
Cedilanid, 0.6 mg. intravenously, 12 hours after 1st test.	2 ml.	As before; duration one minute	None	Cedilanid, 0.2 mg. given intravenously 20 minutes after 2nd test produced in 1½ hours a Wenckebach phenomenon and decreased amplitude of P wave in EKG. Demonstrates quantitation.
Cedilanid, 0.6 mg. intravenously, 20 minutes after 1st test.	None	None	None	Clinically was a question of digitalis intoxication versus decompensation. In and out of hospital for 3 months with varying arrhythmias. Believed to be overdigitalized at time of test. Digitalis increased on basis of test results and patient discharged as improved in 2 weeks.
Cedilanid, 0.6 mg. intravenously, 30 minutes after 1st test.	2 ml.	Wandering sinus pacemaker; duration 2½ minutes plus	None	Demonstrates quantitation.
Cedilanid, 0.6 mg. intravenously, 30 minutes after 1st test.	3 ml.	Pairs of multifocal PVS; duration 5 sec.	None	Subsequently, became toxic on "average digitalizing dose" of digitoxin (1.2 mg. in divided doses in 24 hours). Endpoint appears later than should be expected in retrospect. The apparent myocardial sensitivity for digitalis should have resulted in an endpoint occurring earlier in the test dose schedule.
Cedilanid, 0.7 mg. intravenously, 30 minutes after test.	3 ml.	Wandering sinus pacemaker	None	Demonstrates quantitation.
Digoxin, maintenance dose increased to 0.75 mg./day for 3 days.	3 ml.	Paroxysmal nodal tachycardia; for 3 min. until Na_2EDTA	4.5 ml.	Demonstrates quantitation and sensitivity of test.
Cedilanid, 0.8 mg. intravenously, 45 minutes after test.	2 ml.	Wandering sinus pacemaker with diminution of P Wave; duration 2½ min. plus	None	Demonstrates quantitation and also was used as his own control (Table 3).

* Twenty-four trials of the Calcium-Digitalis Tolerance Test in 15 patients in congestive failure with varying etiologies are summarized above.

A variety of clinical situations are presented. Complemental dosage has been administered with digitalis preparations of varying potency/mg. EKG endpoints are of critical importance and are discussed fully in the text and Figure 2.

verse the EKG endpoint. The Na_2EDTA should be given over a period of at least one minute regardless of the dose required and regardless of the possible emergent nature of the EKG endpoint. Giving the drug more rapidly may cause hypocalcemia, tetany, asystole, and even death. In particular, one should not attempt to correlate the injection of the Na_2EDTA against the EKG endpoint, since there may be a lag of about 20 to 40 seconds between the injection and the ultimate effect of the Na_2EDTA. When used as indicated, the drug is safe and effective.

In this series, Na_2EDTA was generally withheld to determine the duration of benign endpoints (Table 4). It may prove advisable with more experience to administer the appropriate dose of Na_2EDTA routinely within one minute after an endpoint. This would eliminate occasional recurrences of endpoints noted in Table 4.

ELECTROLYTE LEVELS. It was evident in our experimental work that peripheral blood samples for electrolyte levels did not reflect any consistent alteration except hypercalcemia. It has also been shown that when hypercalcemia is induced by injection in dogs the calcium concentration of the blood in the ventricle is twice the concentration in the peripheral blood (Walter and Bowler[10]). So that apparently peripheral blood samples in such a situation are not too significant. It follows that blood samples taken during a simultaneous coronary sinus catherization with the performance of the test would likely reflect significant alterations in the serum electrolytes. This procedure was considered but the facility was not available for reasons beyond our control. Serum electrolyte levels were not determined in this preliminary series of clinical trials for the above reasons.

SIDE REACTIONS TO CALCIUM. With the injection of the higher doses of $CaCl_2$ in some of the patients a warm sensation occurred occasionally in the face and less frequently in the mouth and throat. These sensations were never severe. In several patients there was an urge to micturate before completion of the test. There was no occurrence of thrombosis, slough at the venipuncture site, or paresthesia in the injected extremity in either the test or control groups.

EKG ENDPOINTS. As indicated by Lown and Levine[5,6] digitalis toxicity may be manifested by any supraventricular, nodal or ventricular arrhythmia or disturbance in conduction.

The rapid intravenous injection of large amounts of calcium in nondigitalized persons may produce EKG changes which resemble those commonly called digitalis "effect." These include ST segment depression and sagging, shortening of the QT interval, bradycardia, and accentuation of an existing sinus arrhythmia. Larger doses of calcium, or more rapid injection of the same doses, may produce EKG changes indistinguishable from those commonly associated with digitalis toxicity.

In establishing endpoints which call for the cessation of the test procedure, we have chosen EKG changes which are seen with digitalis intoxication. Thus, the occurrence of rare or infrequent single premature atrial or ventricular extrasystoles are not considered as endpoints. The production of short runs of ventricular extrasystoles (unifocal or multifocal) or ventricular extrasystoles with bigeminy was our most common endpoint, occurring in 6 tests. Four tests produced an endpoint of wandering sinus pacemaker or wandering atrial pacemaker. Three tests demonstrated endpoints of pairs of premature ventricular extrasystoles followed by a short run of nodal

rhythm. Three tests ended with an endpoint of marked diminution or absence of P waves. And in two tests the endpoint was the appearance of first degree heart block. Examples of some of these various endpoints are illustrated in Fig. 2. Other possible endpoints exist which have not been demonstrated in this series.

proved dangerous since succeeding injections evoked an endpoint of ventricular tachycardia, ventricular fibrillation or cardiac asystole. (Also, see the footnote, page 392.)

INDICATIONS. Table 5 summarizes the indications and contraindications for this test at present. Angina pectoris is listed as a contraindication on the basis

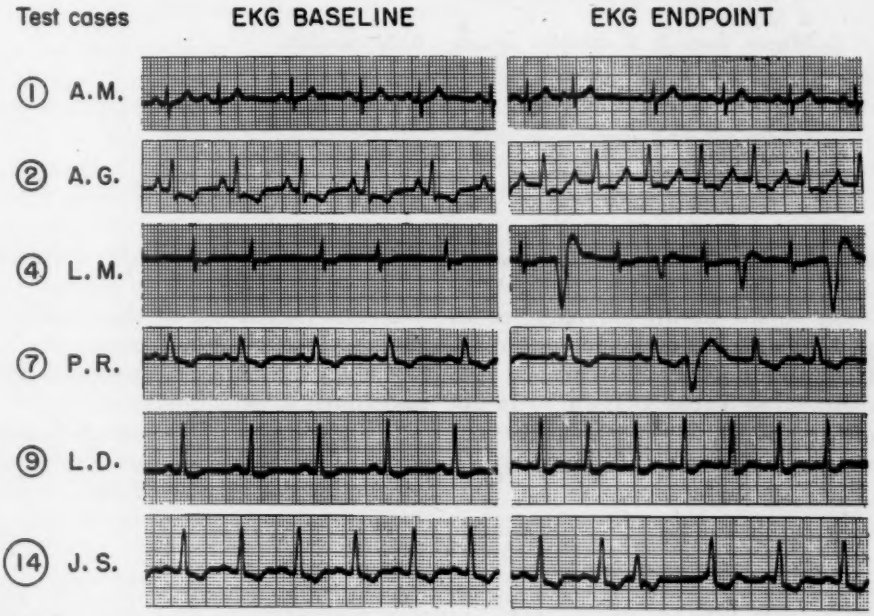

Fig. 2.—A variety of EKG endpoints obtained in this clinical series are illustrated with the corresponding baseline EKG to the left. Reference to Table 4 will identify baseline EKG rhythm and EKG endpoint for each case listed above.

The same EKG change did not always occur as the endpoint in patients who were tested more than one time. On several occasions the exact occurrence of the endpoint was not recognized during the test procedure. Inadvertently, then, the patient received additional unnecessary injections of calcium. In our series this has never proven dangerous, and would seem to be an added safety mechanism, although in the experimental work[7,8] occasionally ignoring an endpoint of Case 5 (Table 3) and the mortality discussed in the footnote (page 392). The increased myocardial sensitivity to calcium and digitalis in myocardial infarction and myocarditis is well-documented.

Summary. 1. The principle and safeguards of the Calcium-Digitalis Tolerance Test are discussed.

2. The technique of the Calcium-Digitalis Tolerance Test is described in detail.

3. The test has been performed 24

TABLE 5.—CALCIUM-DIGITALIS TOLERANCE TEST

Indications	Contraindications
In cases of congestive failure:	
1. Where digitalis effect to maximal levels of tolerance is therapeutically necessary or desirable.	1. Acute or recent myocardial infarction.
2. In acute pulmonary edema with unreliable history of previous digitalization. The test will be useful in detecting a level of digitalization, if any.	2. Angina pectoris.
3. Where there is a question of an arrhythmia due to digitalis intoxication or to decompensation and hypoxia.	3. Myocarditis.
4. Where the adequacy of the maintenance dose of digitalis can be determined.	

times in 15 human beings in congestive failure and the results are summarized in Table 4. Six additional patients in congestive failure were tested in 8 control procedures and the results are summarized in Table 3. There were no complications and no mortality in either the test or control groups.

4. The interpretation of the test data and the computation of the complemental dose of digitalis by a formula is demonstrated.

5. The proper use of the Na_2EDTA, the calcium chelating agent used to reverse persistent or emergent EKG endpoints, is explained.

6. Indications and contraindications in terms of the present level of experience with this test are listed.

ACKNOWLEDGMENTS: We wish to thank O. A. Brines, M.D., Robert Schneck, M.D., Jacob L. Chason, M.D., Abraham Becker, M.D., and L. J. Baer, M.D., for courtesies and services extended to us. Also we are indebted to Gerald C. Timmis, M.D., and Anthony Nolke, M.D., for original contributions to the concept of the calculation of the complemental dose of digitalis.

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(Interlingua on page 390)

EVALUATION OF VALSALVA TEST IN BEDSIDE DIAGNOSIS OF DYSPNEA

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One of the common decisions every practitioner must make prior to instituting therapy is that of the underlying etiology of his patient's complaint of dyspnea. Unfortunately, in evaluating whether or not the symptom of dyspnea is organic, cardiac or pulmonary, or is functional, the physician frequently finds himself confronted with a diagnostic dilemma not readily resolved even after careful examination, particularly in atypical and borderline cases. Indeed, since most of the ancillary aids useful for clarification of such situations either require specialized equipment not readily available and delay (roentgenologic and laboratory data) while other procedures (circulation time, vital capacity, venous pressure determinations) are often unreliable due to subjective error or are cumbersome to perform; an easy, reliable objective test easily done at the bedside has long been sought. Although in the past the physiologic responses to the Valsalva maneuver (controlled forced expiration) have been extensively studied in both normal individuals and in patients suffering from various forms of myocardial and valvular disease (Elisberg *et al.*[1], Goldberg, Elisberg and Katz[2], Greene and Bunnell[3], Hamilton, Woodbury and Harper[4], Price and Conner[8], and Stanley, Hardenbergh and Whittenberger[9]), it was only recently that Knowles, Gorlin and Storey[5,6,7] developed this procedure as a practical clinical test. These workers indicated that this procedure would be especially of value in pinpointing the etiologic mechanism in the less overt case of pulmonary congestion before typical and classical physical findings become manifest. For this reason 60 patients whose chief complaint was primarily that of dyspnea were studied utilizing the Valsalva test in an attempt to ascertain the clinical reliability and diagnostic value of this maneuver as a routine diagnostic procedure in the hands of the practicing physician.

Methods. Without entering into a detailed discussion of the basic physiologic background of the Valsalva maneuver which has previously been reported in detail in the literature (Knowles, Gorlin and Storey[5,6]), a brief description of the equipment needed, technique and different responses in both normal and disease states is in order.

First, the equipment needed to perform the test may be easily carried in every physician's bag. All that is necessary is an aneroid sphygmomanometer gauge attached to a short length of rubber tubing onto which is fitted a mouthpiece. The other items required are an ordinary blood pressure apparatus and a stethoscope.

The Valsalva maneuver is performed by placing the patient supine and, after a short rest period, determining the resting systolic blood pressure. Having done this, the manometer gauge attached to the tubing fitted with a mouthpiece is handed to the patient who holds the manometer dial in one hand at a level where he can see the pointer, while the mouthpiece is placed in his mouth. Instructions are given that upon command

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he will expire with sufficient vigor to force the manometer pointer to 40 mm. Hg which he will then steadily maintain until told to breathe normally. One or two trials will rapidly demonstrate the desired technique. The patient must elevate the needle rapidly, not slowly, and keep it at 40 mm. Hg for approximately 10 seconds. By gradually expiring, thus delaying the rapid attainment of 40 mm. Hg, a false result may be forthcoming. Prior to initiating the forced expiration the patient is instructed to take only a normal breath, not an abnormally large inspiration which also may produce a false reading.

normal respiration followed by a period of bradycardia (see Fig. 1). The observation of Phases 1 and 4 is all that is necessary when recording the Valsalva response at the bedside. After the initial arterial pressure spike is noted, the sphygmomanometer cuff is deflated to 10 to 15 mm. Hg above the original resting pressure, the patient instructed to resume normal breathing, and then the rebound or overshoot is noted.

Now in contrast to this normal response, characterized by an initial blood pressure spike and followed by an overshoot once expiratory effect has ceased, when sufficient

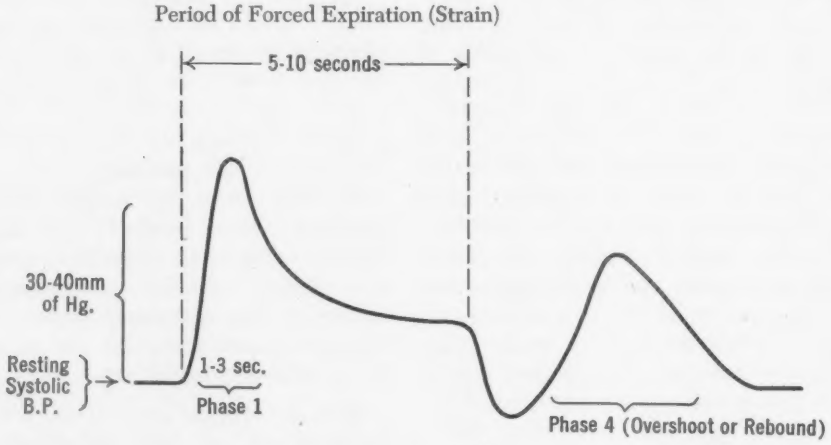

Fig. 1.—Schema of blood pressure response in negative (Normal) Valsalva test.

The practitioner next sets the level of the blood pressure dial attached to the arm at approximately 30 to 40 mm. Hg above the previously determined resting systolic pressure. Then the patient is told to expire, as described above, for about 10 seconds and then resume normal breathing. This produces the 4 phases of the Valsalva response.

In a normal individual the 4 phases will develop as follows: Phase 1 (strain phase): this consists of an initial rise of systolic pressure which is transiently heard 30 to 40 mm. Hg above the resting systolic pressure for from 1 to 3 seconds; Phase 2 is a gradual fall of systolic pressure occurring while expiration is maintained; Phase 3 is a further rapid transient drop of systolic pressure occurring when patient resumes normal breathing; and, Phase 4 is a rebound (overshoot) of the systolic pressure to 10 to 15 mm. Hg or more above the resting systolic pressure occurring 3 to 8 seconds after resumption of

pulmonary congestion produced by left ventricular failure, mitral stenosis (with or without failure), aortic stenosis, combined right and left ventricular failure, pure right ventricular failure or constrictive pericarditis is present, a totally different and easily recognized arterial pressure pattern is usually found on doing the Valsalva test. Under these circumstances following forced expiration, again maintained at 40 mm. Hg for 10 seconds, the initial systolic rise in pressure is sustained throughout the entire period of expiratory strain (Phase 1), rather than being transient as in the normal patient. Secondly, the arterial overshoot or rebound normally occurring following cessation of expiration usually fails to appear (see Fig. 2).

In the study presented here the normal duration of the initial arterial spike was considered to be anything under 3 seconds, followed by an overshoot, while the abnormal arterial response was a systolic plateau of 5

seconds or longer usually not followed by a rebound. Equivocal responses were considered to be indicated by an elevation of the primary systolic rise for 3 to 5 seconds with an absent or minimal overshoot (see Fig. 3).

Sixty patients who complained primarily of varying degrees of dyspnea comprise the case material of this series. Each patient had a complete history and physical examination, blood count, urinalysis, chest roentgenogram, electrocardiogram, daily weight, vital capacity, circulation time (Decholin: arm to tongue), and a test dose of Thiomerin. The Valsalva test was done by one or more observers (R.W.A., R.H.T., B.E.E.), with the patient supine and in most instances prior to the administration of specific therapy.

Results. As will be noted in the accompanying Table 1 (A, B, C), a wide variety of cardiac and pulmonary disease was studied. In a good number of these cases the problem consisted of deciding whether a minimal degree of cardiac failure was being masked by the obvious presence of moderate to marked pulmonary emphysema or other pulmonary abnormalities. For

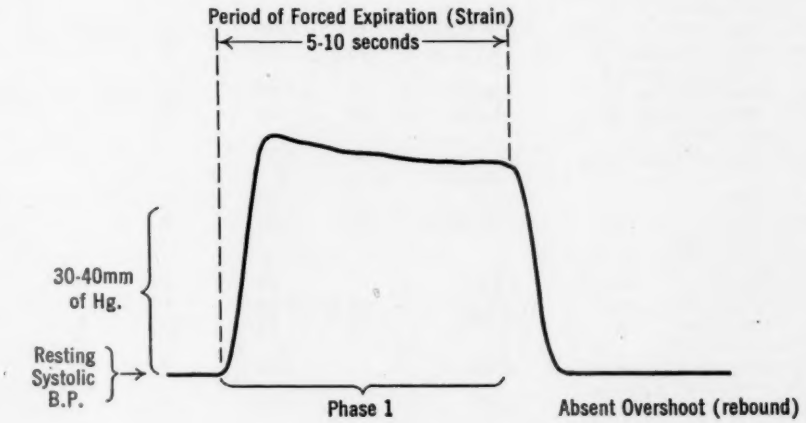

Fig. 2.—Schema of blood pressure response in positive (Abnormal) Valsalva test.

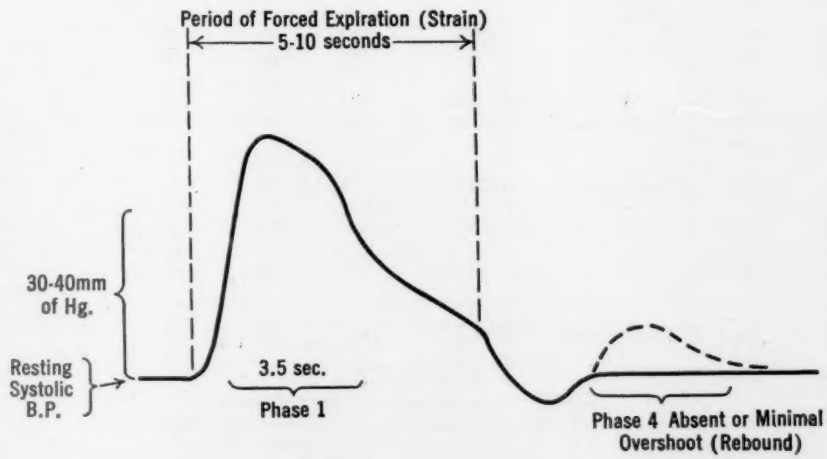

Fig. 3.—Schema of blood pressure response in borderline (Equivocal) Valsalva test.

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TABLE 1-A.—POSITIVE (ABNORMAL) VALSALVA TEST GROUP

No.	Valsalva		Roentgenogram	EKG	Circ. time (sec.)	Vital Cap. %	Wt. loss after Thiomerin (lb.)	Diagnosis
	Result (sec.)	Rebound						
1.	8	No	Enl. heart	PWNL	Not recorded	57	4	ASHD, Class III Emphysema
2.	9	No	Enl. heart	LVH	60+?	96	2	RHD with AI and probable MS, Class II
3.	10	No	Enl. heart	LVA	16	54	Contra-indicated	AI following acute bact. endocarditis. Not ambulatory.
4.	8	No	Ht. upper normal in size	AF LVA	30	80	30	ASHD with AF, Class IV
5.	10	No	Enl. heart	LVH	25	68	6	ASHD, Class III
6.	10	Yes	Enl. left ventricle	LVH	35	76	11	AI, Luetic, Class III
7.	10	No	Enl. heart	LVA	45	75	0	Ht. disease undiag. with MI, Class III
								CVA with left hemiparesis
8.	10	No	Emphysema	N	31	76	0	Emphysema, ASHD with mild failure
9.	10	No	Enl. heart	PWNL	18	28	38	ASHD, Class IV
10.	10	No	Bilat. pl. effusion	LVA	18	35	11	ASHD, Class III
11.	6	No	Enl. RV	RVH	17	79	10	RHD with MS, Class I
12.	7	No	Enl. heart	LVH	28	60	17	HCVD (malignant phase)
13.	8	No	Enl. heart	LVA and infarct	32	73	5	ASHD with failure
14.	10	No	N	N	16	93	0	RHD with MS, Class I
15.	8	No	N	Inc. RBBB	120?	64	3	ASHD with auric. flutter-fibr. Emphysema
16.	8	No	N	LVA	17	58	3	ASHD, Class III?
17.	7	No	N	PWNL	22	80	1½	HCVD, Class II
18.	5	No	N	RBBB	30	61	10	ASHD, Class II? Diabetes mellitus
19.	7	Yes	Upper normal in size-ht.	N	17	91	4	ASHD with anginal syndrome, Class II
20.	5	No	Enl. heart	N	60+	74	7	Angioneurotic edema, chronic
21.	6	Yes	N	LVH atrial hypertrophy	18	76	2	RHD with AI and AS, Class II
22.	6	No	Borderline enlargement	AF		52	6½	ASHD, Class III
23.	5	No	Enl. LV	PWNL	70	72	5	HCVD & ASHD, Class I
24.	5	No	N	PN	16	63	0	ASHD with mild failure), Class II
25.	5	No	N	LVA, AF	22	55	4	ASHD, Class III
26.	5	No	Emphysema	P. pulm.	19	73	3	Emphysema, chronic bronchitis, early cor pulmonale?
27.	5	No	Emphysema	RBBB	Unsatisfactory	42	7	Emphysema, ASHD, asthmatic bronchitis
28.	5	No	N	PWNL	28	57	5	HCVD with congestive failure, Class III
29.	10	No	N	AF, VPC's	23	44	5	ASHD with pulmonary emphysema. Subacute bronchitis.
30.	7	No	Emphysema	PWNL	16	46	5	ASHD with failure, Emphysema, Class III

AF = Atrial fibrillation
ASHD = Arteriosclerotic heart disease
HCVD = Hypertensive cardiovascular disease
LVA = Left ventricular abnormality
N = Normal
PWNL = Probably within normal limits
RBBB = Right bundle branch block
RVH = Right ventricular hypertrophy
RHD = Rheumatic heart disease
VPC = Ventricular premature contraction

TABLE 1-B.—NEGATIVE (NORMAL) VALSALVA TEST GROUP

No.	Valsalva: Result (sec.)	Valsalva: Rebound	Roentgenogram	EKG	Circ. time (sec.)	Vital Cap. %	Wt. loss after Thiomerin (lb.)	Diagnosis
1.	2	Yes	N	N	18	80	4	Pulmonary emphysema Ess. hypertension
2.	3	Yes	N	N	19	90	4	ASHD, Anginal syndrome. Hiatus hernia.
3.	2	Yes	Emphysema	LAD Nonspecific ST changes	17	81	4	Pulmonary emphysema
4.	2	Yes	Emphysema	N	120+	32	0	Pulmonary emphysema
5.	2	Yes	N	N	13	89	0	Allergic bronchitis
6.	2	Yes	N	N	15	67	2	Obesity, alcoholic neuritis
7.	3	Yes	N	PWNL	15	76	3	Diabetes, ASHD compensated
8.	3	Yes	Emphysema	N	45	37	0	Laennec's cirrhosis, emphysema, chronic bronchitis
9.	2	Yes	Emphysema	PWNL	18	93	4	ASHD with anginal syndrome, pulmonary emphysema
10.	2	Yes	Bullous emphysema & apical fibrosis	N	18	64	0	Pulmonary emphysema
11.	3	Yes	N	N	15	48	0	Pulmonary emphysema & bronchitis
12.	3	Yes	N	PWI	37	78	Not recorded	HCVD and acute myocardial infarction
13.	3	Yes	N	P. pulmonale	18	60	0	Emphysema; chronic bronchitis
14.	2–3	Yes	N	N	20	72	0	Subacute bronchitis
15.	2–3	Yes	N	N	16	76	3	Postural hypotension Bronchiectasis
16.	3	Yes	N	N	14	91	Not recorded	Emphysema, arteriosclerosis
17.	2	Yes	N	LVA	16	52	0	Pulmonary emphysema
18.	2	Yes	N	WNL	18	102	0	Venous insufficiency of legs, obesity
19.	Neg.	Yes	Diffuse miliary calcification	PWNL	25	60	2	Pulmonary emphysema, chronic bronchitis, poss. healed histoplasmosis
20.	3½	Yes	N	PN	18	75	1	RHD with MS, Class I
21.	2	Yes	Emphysema	P. pulmonale	15	67	Not recorded	Emphysema, asthmatic bronchitis
22.	2	Yes	N	VPC & WNL	17	57	0	Obesity & anxiety
23.	1½	No	N	Not obtained	18	40	0	Asthmatic bronchitis
24.	2	Yes	N	WNL	18	56	3	Emphysema
25.	3	No	Pulmonary emphysema	LAD PWNL	15	66	4	Portal cirrhosis with ascites
26.	2	Yes	Pulmonary emphysema	WNL	19	70	4	Essential hypertension, obesity

ASHD = Arteriosclerotic heart disease
HHD = Hypertensive heart disease
LAD = Left axis deviation
LVA = Left ventricular abnormality
N = Normal
PWI = Posterior wall infarct
PWNL = Probably within normal limits
RHD = Rheumatic heart disease
VPC = Ventricular premature contraction
WNL = Within normal limits

this purpose the Valsalva test was found to be of considerable value in contrast to the commonly employed aids previously relied on, such as circulation time, vital capacity, diuretic response, and venous pressure.

Out of the 60 patients subjected to the Valsalva test a positive response was obtained in a total of 30 cases; a negative reaction in 26 instances; and an equivocal pattern (initial plateau 3 to 5 seconds with or without a minimal overshoot) in 4 individuals.

pulmonary artery pressure if the mitral orifice is sufficiently narrowed. Because of this fact the test may be of aid in evaluating the presence and severity of mitral valvular disease (Knowles, Gorlin and Storey[6]) both before and after valvulotomy. Another of the patients with a positive Valsalva test was an individual with aortic insufficiency resulting from an attack of acute bacterial endocarditis. This man also had a mitral diastolic murmur that was believed to be either relative (Austin

TABLE 1-C.—EQUIVOCAL (BORDERLINE) VALSALVA TEST GROUP

No.	Valsalva Result (sec.)	Valsalva Rebound	Roentgenogram	EKG	Circ. time (sec.)	Vital Cap. %	Wt. loss after Thiomerin (lb.)	Diagnosis
1.	4	Yes	Emphysema	1° AV block	14	48	4	Emphysema, chronic bronchitis, ASHD
2.	4	Yes	Cardiomegaly	N	17	68	3	Pulmonary emphysema ASHD, essential
3.	2–3	No	N	Old PWI LVA	20	50	3	Emphysema & bronchitis ASHD, old fracture of T_{11}
4.	4	Yes	N	WNL	13	91	2	Mild emphysema, bleeding peptic ulcer

N = Normal
LVA = Left ventricular abnormality
PWI = Posterior wall infarct
WNL = Within normal limits

Correlating the tests with the evidence of clinical congestive failure as judged by the physical findings, response to diuretics, diminution of heart size and alleviation or improvement in symptomatology, particularly that of dyspnea on exertion, it was found that 86.6% of the positive Valsalva group were felt to have definite degrees of heart failure.

Of the 4 patients with positive Valsalva responses who were judged not to show evidence of cardiac failure, one had uncomplicated mitral stenosis which, as has been previously shown (Elisberg *et al.*[1] and Knowles, Gorlin and Storey[5,6]), will produce an abnormal Valsalva test due to increased

Flint) mitral stenosis or possibly a true mitral stenosis resulting from the endocarditis. The third positive was a patient in whom early cor pulmonale was suspected but not proved. Response to digitalization in this case was questionable although the patient thought he was slightly improved. In the fourth patient who had a positive test with no confirmatory evidences of failure, the problem was one of evaluation of an extremely hostile psychopathic personality type who could not be relied upon with respect to history. This case is considered as a failure (see Table 2).

Both the circulation time and diuretic response to Thiomerin were found to correlate poorly with respect to the pa-

tients having a positive Valsalva response. There were 37% of those with a positive test who had an arm to tongue circulation time within normal limits, (20 seconds or less), and only 50% lost more than 5 pounds of weight following the test dose of Thiomerin. congestive heart failure or valvular disease. In 80.7% of the negative group the circulation time was within normal limits with only 11.5% having prolonged times. With respect to diuresis, 100% of the negative Valsalva patients lost less than 5 pounds (see Tables 3 and 4).

TABLE 2.—CORRELATION OF VALSALVA TEST WITH FINAL DIAGNOSIS

	Positive	*Negative*	*Equivocal*
Congestive Heart Failure	26 (86.7%)	0	2 (50%)
Not in Congestive Heart Failure	4 (13.3%)	26 (100%)	2 (50%)
Total	30 (100%)	26 (100%)	4 (100%)

TABLE 3.—CORRELATION OF VALSALVA TEST WITH CIRCULATION TIME

	Positive	*Negative*	*Equivocal*
Circulation Time (20 sec. or less)	11 (37%)	21 (80.7%)	4 (100%)
Circulation Time (20 sec. or more)	13 (43%)	3 (11.5%)	0
Unsatisfactory	6 (20%)	2 (7.7%)	0
Total	30 (100%)	26 (100%)	4 (100%)

TABLE 4.—CORRELATION OF VALSALVA TEST TO DIURETIC RESPONSE

	Positive	*Negative*	*Equivocal*
Weight Loss Less Than 5 Pounds	10 (33.3%)	26 (100%)	0
Weight Loss More Than 5 Pounds	15 (50%)	0	4 (100%)
No Response	3	0	0
	– (16.7%)	0	0
Contraindicated	2		
Totals	30 (100%)	26 (100%)	4 (100%)

These results stress the unreliability of these methods in evaluating the presence of minimal pulmonary congestion of cardiac origin.

A total of 26 patients had a negative Valsalva test and none of these individuals was found to have any clinical, laboratory or therapeutic findings that indicated cardiac disease with pulmonary congestion as the cause of their dyspnea. In other words, this entire group (100%) showed no evidence of

Finally, in the equivocal group of 4 cases, it was concluded that 2 definitely were in congestive failure, while the other 2 were not. All 4 of these patients had normal circulation times; however, in contrast, all of them had a positive response to Thiomerin with a weight loss greater than 5 pounds. One of these individuals was an elderly man suffering from dyspnea caused by pulmonary emphysema complicated by hypochromic anemia (7

gm. Hb.) resulting from a slowly bleeding marginal ulcer. After blood transfusion a repeat Valsalva test was negative. Another positive case who had no supportive evidence of pulmonary congestion was a man with essential hypertension and far advanced pulmonary emphysema. Therapeutic trial of digitalis failed to afford any relief of his dyspnea. The 2 patients with equivocal Valsalva tests who were partially relieved by digitalis, low salt diet, and diuresis were cases later proved to have both pulmonary emphysema and incipient cardiac failure. In these 2 patients, the Valsalva test failed to clarify the diagnosis.

Since the purpose of this study was to evaluate the accuracy of the Valsalva test in the differential diagnosis of dyspnea, no attempts were made to repeat the maneuver once clinical improvement had been obtained following therapy in the positive group. However, it has been reported that, as the degree of pulmonary congestion decreases due to specific therapy (digitalis, bed rest, and the like) the Valsalva test frequently will revert from a definite positive to either an equivocal or negative pattern and, thus, may be used as a guide to the efficacy of the treatment being employed (Knowles, Gorlin and Storey[6]). This seemed to be the case in the few patients on whom it was attempted and further evaluation is being conducted along this line.

Discussion. First, it should be emphasized that it is not the purpose of the authors to convey that the Valsalva test alone is a foolproof guide to the presence or absence of varying degrees of pulmonary congestion resulting from the cardiac causes previously discussed. It is, however, our firm impression after utilizing this diagnostic technique over a considerable period of time that once experience is gained in its performance this simple test can be extremely useful. Since it can be done quickly at the bedside with minimum equipment, it is of particular value. Further, the results in the majority of instances are usually clear-cut and objective. In the small percentage of cases where an equivocal response is obtained, the test should be repeated after mild exercise, if it is thought the patient can tolerate this, or, with the legs raised on a pillow. These measures may change an equivocal test to a positive one. If not, the test usually proves not to be of significance.

It has been suggested too that this procedure is one way of determining the efficacy of mitral valvulotomy. The reader is referred to the work of Knowles, Gorlin and Storey[6] for details since the authors had no opportunity to evaluate the Valsalva maneuver before and after mitral surgery. However, both of the patients with mitral stenosis who were studied did have positive tests. One of these patients was not in clinical failure indicating that his pulmonary artery pressure was significantly elevated although he had not yet reached the stage of actual pulmonary congestion or edema.

Before attempting to incorporate this test into one's diagnostic kit, the physician should gain experience on known normals. After a few trial runs, the ease with which this procedure can be done should be self-evident. Several errors in technique should be guarded against in that they may render the test inaccurate. If the airway pressure is elevated too slowly or is of insufficient initial force to maintain the manometer at 40 mm. Hg, a false positive test may result. Again, if the airway pressure is allowed to diminish after the initial level of 40 mm. Hg is reached, a false negative test may be obtained. These mistakes

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are easily avoided by having the patient practice the technique beforehand. It should be mentioned though that if the patient is of low mentality he may not be able to follow instructions well enough to successfully perform the maneuver. In most cases this is not a problem.

Our results indicated poor reliability of the circulation time and response to a test dose of mercurial diuretic in the group of patients who definitely were shown to have congestive heart failure of minimal or more advanced degree. All of these patients, in contrast, did have a positive Valsalva response and all were relieved following digitalization.

Another sphere of usefulness for the Valsalva test which has been suggested is the pre-operative evaluation and postoperative follow-up of patients in whom the cardiac reserve is considered borderline. In the elderly patient this test would be of help in distinguishing between the dyspnea resulting from pre-existing pulmonary damage and the early onset of incipient congestive failure precipitated by operative or postoperative stress. Again regular preoperative use of the test may disclose cases of minimal pulmonary congestion which might have otherwise gone unrecognized with subsequent unwanted sequelae developing; for example, acute operative or postoperative pulmonary edema.

Summary and Conclusions. The Valsalva test was performed on 60 patients with various types of pulmonary and cardiac disease. It was found that this simple objective test provided reliable information as to the presence of varying degrees of pulmonary congestion resulting from cardiac dysfunction since in the majority of positive cases the cause of dyspnea was subsequently proved to be due to cardiac failure as judged by response to digitalization, decrease in heart size, diuresis and disappearance or diminution of clinical signs and symptoms. The Valsalva test, as here described, was felt to be especially useful in demonstrating incipient cardiac failure in complicated and borderline cases where clinical evaluation and ancillary aids such as circulation time, response to diuresis and vital capacity were equivocal or of no value. Again a negative Valsalva test was found to indicate that the etiology of the patient's dyspnea was due to pulmonary disease rather than cardiac failure in all instances.

Since the Valsalva test requires only minimal equipment, can be readily learned and utilized also by nurses or intelligent office personnel, and is more reliable yet less time-consuming than other techniques commonly used to evaluate cardiac and pulmonay function, it is suggested that this test be more widely employed in the differential diagnosis of dyspnea. Due to its simplicity, the Valsalva test is of particular value to the practicing physician for use at the bedside.

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SUMMARIO IN INTERLINGUA

Evalutation del Experimento de Valsalva Como Practic Test Clinic in le Diagnose de Dyspnea

Le experimneto de Valsalva esseva effectuate in 60 patientes con varie typos de morbo pulmonar e cardiac. Esseva constatate que iste simple e objective manovra provideva exacte informationes quanto al presentia de varie grados de congestion pulmonar como resultato de dysfunction cardiac, proque in le majoritate del casos positive il esseva demonstrate subsequentemente que le dyspnea esseva causate per insufficientia cardiac, manifeste in le responsa a digitalisation, in reducite dimensiones del corde, in diurese, e in le disparition o diminution de signos e symptomas clinic. Le experimento de Valsalva, in le forma hic describite, esseva considerate como specialmente utile in le demonstration de incipiente insufficientia cardiac in casos complicate o marginal in que le evalutation clinic e observationes ancillari, del tempore circulatori, del responsa a diurese, del capacitate vital, etc., esseva sin valor o de valor indecise. Del altere latere, il esseva constatate que le experimento de Valsalva indica per su negativitate que le etiologia del dyspnea del patiente implica un morbo pulmonar plus tosto que insufficientia cardiac. In le serie hic reportate, iste observation valeva sin exception.

Proque le experimento de Valsalva require un minimo de apparatura, proque illo es facile a apprender de maniera que illo pote esser utilisate per infirmeras e intelligente membros del personal administrative, e finalmente proque illo es plus exacte sed minus lente que le altere technicas que es usate communmente pro evalutar le function cardiac e pulmonar, il es proponite que iste test es usate plus extensemente in le diagnose differential de dyspnea. In consequentia de su simplicitate, le experimento de Valsalva es de valor particular pro le medico practic qui pote effectuar lo durante su visita al domicilio del patiente.

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ANALGESIC EFFECTIVENESS OF ORALLY ADMINISTERED ETHOHEPTAZINE IN MAN

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The purpose of this report is to present further data as to the analgesic effectiveness and safety of a new synthetic compound. In 1954, Seifter *et al.*[5] reported that seven-membered ring analogs of meperidine possessed unusual properties. Chemically they differed from meperidine in replacement of the piperidine ring structure by hexamethylenimine. Pharmacologically, one of these compounds, known generically as ethoheptazine, in addition to its analgesic properties differed from other potent analgesics in that it (1) did not provoke morphine-like excitement in cats, (2) did not cause lethargy in rats, (3) did not, in animals, depress respiratory function before circulatory failure, and (4) antagonized the action of barbiturates 24 hours after their administration to rats. Studies in man (Grossman *et al.*[4]) indicated that ethoheptazine, namely, 1-methyl-4-carbethoxy-4-phenyl hexamethylenimine, was most suitable for continued investigation. A dose of 50 to 100 mg. administered orally appeared to be most effective and safe. The utilization of this compound known as ethoheptazine* was evaluated in 4 groups of patients requiring analgesics for a wide variety of medical and surgical conditions. It was also possible in 2 groups of patients to compare the effectiveness of ethoheptazine when administered concomitantly with aspirin.

Selection of Patients and Procedure. As indicated previously (Batterman[1]), the appraisal of new drugs for the clinical relief of pain must adhere to conditions under which these drugs will actually be used by the general practitioner. It is for this reason that this study was done on both ambulatory and hospitalized patients with consideration of effects related to dosage and duration of therapy. No attempt was made to select patients on the basis of diagnosis, severity or duration of the painful state. The analgesic response was based on 3 factors: the degree of pain relief, the occurrence of untoward reactions and the over-all response

*Wyeth Laboratories, Philadelphia, Pa., graciously supplied us with the medication and gave other aid in connection with this investigation.

for the entire period of observation. A satisfactory analgesic response had to result in "complete" or "moderate" relief, based on criteria reported previously (Batterman[2]). Complete analgesia represented the subjective obliteration of pain for a minimal period of 3 hours with little if any untoward reaction interfering with the continuation of therapy. A moderate response indicated that there was either a partial relief for 3 hours or longer, or complete relief for 2 to 3 hours, or that the occurrence of undesirable untoward reactions prevented satisfactory clinical control of the patient in spite of complete analgesia. Any slight analgesia or occurrence of pain relief with concomitant severe untoward reactions were considered unsatisfactory and, therefore, insignificant. In view of the subjectivity of the problem, these criteria were adhered to very rigidly. There was no question in any of the patients reporting satisfactory analgesia that clinical control was achieved. A satisfactory response had to be present during the entire period of observation and not only with an isolated drug administration. If at onset of therapy, the response was favorable but with continued therapy, the patient's pain was not adequately controlled, then the trial was considered entirely unsatisfactory. The same consideration was given to the occurrence of untoward reactions. To be significant, they had to occur as a repeated event in the majority of all instances of drug use.

Results. AMBULATORY PATIENTS. There were 107 ambulatory patients ranging in age from 16 to 80 years. There were 68 females and 39 males. The duration of therapy ranged from a single dose to 10 weeks. Fifty per cent of the patients were treated for 2 weeks or longer and 25% were treated for 3 weeks or longer. The patients were advised to take one tablet equivalent to 50 mg. every 4 hours for 4 daily doses. Table 1 summarizes the results in this ambulatory group of patients. Satisfactory analgesia regardless of etiology of the painful state was achieved in 78 of the 107 patients for an incidence of approximately 73%. Experience (Batterman and Grossman[3]) with salicylates and placebo therapy in a similar group of patients resulted in satisfactory analgesia in 52% and 46%, respectively. The majority of patients in the present series were sufferers from musculoskeletal complaints. This is in accord with the fact that ambulatory patients with chronic pain are more apt to have an arthritic condition as an etiology for their disability. From the predictability point of view, therefore, ethoheptazine was very satisfactory in patients with exception of those with rheumatoid arthritis. The presence of an acute inflammatory exudative process in such patients limits the value of a pure analgesic drug. However, it is noted that even in these patients, satisfactory analgesia occurred in the majority. In a small group of medical conditions such as gastrointestinal, cardiac and renal, the majority of patients also responded. The occurrence of mild and insignificant untoward reactions was noted in 4 patients for an incidence of approximately 4%. These took the form of anorexia, nausea or dizziness.

HOSPITALIZED PATIENTS. Two groups of hospitalized patients from either an acute or a chronic disease institution were studied. There were 140 patients ranging in age from 18 to 92 years. There were 58 males and 82 females. The duration of therapy ranged from one to 285 days. Sixty-nine patients (49%) were treated for one week or less. Forty-three (31%) were treated for 3 weeks or longer and 10 patients (7%) were treated for more than 3 months. Approximately 14,000 doses were observed. The number of doses varied from 2 to 1012 with 50% of the patients receiving 20 or more doses; 25% of the patients 100 or more doses; and 5% of the patients 500 or more doses. Two dosage levels were used, 50 or 100 mg. administered orally, p.r.n., 4 times daily or every 4 hours. There was a total of 163 trials of therapy with 23 patients studied under

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TABLE 1.—ANALGESIC EFFECTIVENESS OF 50 MG. ORALLY OF ETHOHEPTAZINE IN AMBULATORY PATIENTS

Diagnosis	*Number of Patients*	*Analgesic Effectiveness*						
		Complete	*Moderate*	*Satisfactory %*	*Slight or None*		*Untoward Reactions*
					No.	*%*	
Osteoarthritis	30	12	9	70	9	30	
Rheumatoid Arthritis	20	5	8	65	7	35	
Myositis, Fibrositis, Myalgia	22	9	8	77.3	5	22.7	3
Ligamental Strain, Sciatica	8	6	2	100.0	–	–	1
Bursitis	5	3	1	80.0	1	20.0	
Menopausal Arthralgia	5	–	4	80.0	1	20.0	
Miscellaneous	17	3	8	65.0	6	35.0	
Total	107	38 (35.5%)	40 (37.4%)	72.9	29	27.1	4 (3.79%)

TABLE 2.—ANALGESIC EFFECTIVENESS OF ETHOHEPTAZINE ADMINISTERED ORALLY IN HOSPITALIZED PATIENTS

Dose mg.	*Number of Trials*	*Analgesic Effectiveness*					*Untoward Reactions*	
		Complete	*Moderate*	*Satisfactory %*	*Slight*	*None*	*No.*	*%*
50	58	12	16	48.2	10	20	0	0
100	105	35	30	61.8	6	34	4	3.8

both dosage levels. The results are summarized in Table 2. Regardless of etiology for the pain in hospitalized patients, 50 mg. is unsatisfactory for control of the patients' complaints. However, 100 mg. studied in 105 patients gave satisfactory analgesia in 62% of the trials. When considered in terms of diagnosis (Table 3) it is again apparent that the greatest effectiveness was in the relief of musculoskeletal pain usually associated with arthritis. When neoplastic disease was early and the severity of the pain did not require injectable potent analgesics, then 50% of the patients had satisfactory analgesia. In the terminal phase of the disease, there was no response and there was no decrease in the requirements of the more potent analgesics. The medication was ineffectual in any condition with severe pain where ordinarily morphine or meperidine would be required. Thus in renal disease or myocardial infarction, there was no effective relief of pain. Headaches, which made up a good number of the miscellaneous patients were also unresponsive. A satisfactory response was obtained in neurologic patients with neuritis, tabes dorsalis and postoperative or surgical patients with mild pain. Untoward reactions as in the case of ambulatory patients occurred in 4 patients for an incidence of approximately 4%. These consisted of nausea or dizziness and were insignificant.

The over-all response of 62% was similar to our experiences with codeine, but the amazingly low incidence of untoward reactions and the lack of cumulative toxicity favored ethoheptazine over codeine. Patients with chronic administration continued to maintain satisfactory analgesia without evidence of tolerance. There was no disturbance in bowel or urinary function. There was no depression of the cough reflex, sedation or other reactions commonly associated with analgesics of this potency.

POSTPARTUM PAIN.* Eighty-three women received 100 mg. of ethoheptazine every 4 hours for postpartum pain. The number of doses ranged between one and 10. Satisfactory control of abdominal or perineal pain, or both, was achieved in 82% of the trials. This was approximately 20% higher than our experience with combined codeine and aspirin for the same situation. None of these patients presented any untoward reaction.

COMBINATION WITH ASPIRIN. The effectiveness, tolerance and safety of the administration of combined ethoheptazine and aspirin were studied in 2 groups of patients. The first group of patients consisted of 66 subjects. All were ambulatory and presented varying degrees of pain due to a variety of musculoskeletal conditions. The patients were advised to take 50 mg. of ethoheptazine simultaneously with one tablet or capsule of aspirin equivalent to 300 mg. (5 grains). In no instance was the patient aware that aspirin was being dispensed. The medication was taken 4 times daily for periods ranging from 2 days to 12 weeks. In 3 instances, where the medication was taken for less than a week, it was discontinued on the patients' own accord because of the occurrence of some untoward reaction. With this exception, the majority of patients received the medication for several weeks. The results are summarized in Table 4. The over-all response for the combination and for ethoheptazine alone is identical (see Table 1). There is, however, a striking change in the group of patients with

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TABLE 3.—ANALGESIC EFFECTIVENESS OF 100 MG. ETHOHEPTAZINE ADMINISTERED ORALLY IN HOSPITALIZED PATIENTS

Diagnosis	Number of Patients	Analgesic Effectiveness					Untoward Reactions
		Complete	Moderate	% Satisfactory	Slight or None		
					No.	%	
Neoplasms	28	5	9	50.0	14	50.0	1
Arthritis	29	14	9	79.3	6	20.7	1
Postoperative	6	5	1	(100.0)	–	——	
Surgical	6		4	——	2	——	
Renal	5	1		(20.0)	4	(80.0)	
Medical	16	5	5	62.5	6	37.5	1
Neurologic	5	3	1	(80.0)	1	(20.0)	
Miscellaneous	10	2	1	30.0	7	70.0	1
Total	105	35	30	61.8	40	38.2	4 (3.8%)

TABLE 4.—ANALGESIC EFFECTIVENESS OF 50 MG. OF ETHOHEPTAZINE AND 300 MG. OF ASPIRIN IN AMBULATORY PATIENTS

Diagnosis	Number of Patients	Complete	Moderate	% Satisfactory	Slight or None		Untoward Reactions
					No.	%	
Osteoarthritis	25	7	10	64	8	36	2
Rheumatoid Arthritis	21	6	13	90	2	10	2
Myositis, Fibrositis, Myalgia	3		2	66	1		1
Ligamental Strain, Sciatica	2			—	2	—	
Bursitis	2		1	—	1		1
Menopausal Arthralgia	8	3	1	50	4		1
Miscellaneous	5	1	2	60	2		1
Total	66	17 (25.7%)	29 (43.9%)	69			8 (12%)

rheumatoid arthritis. Ethoheptazine alone, lacking any anti-inflammatory properties was not as satisfactory as when combined with salicylates. This reflects the principles of combined analgesic therapy that unless a specific type of pain is present, the over-all potency of the mixture is dependent upon the most potent of the analgesic agents. Aspirin alone, for the same patient, is no more effective than 55%. A combination, in certain patients, is better than either one alone since the pain may be alleviated as the result of combined mechanisms of action. In terms of toxicity, the mixture is approximately the same as ethoheptazine alone and for all practical purposes, may be stated to possess very little or few untoward reactions. The incidence of 12% is still within the range noted with placebo therapy. Untoward reactions were minimal and took the form of nausea, epigastric burning or headache and in only 3 instances did the patient discontinue the medication because of their occurrence.

The second group of patients consisted of 61 postpartum women who received 100 mg. of ethoheptazine and 600 mg. (10 grains) of aspirin every 4 hours as necessary after delivery. The number of dosages ranged between one and nine. The results were superior to that noted with ethoheptazine alone since every patient had satisfactory control of abdominal or perineal discomfort, or both, without occurrence of any untoward reaction.

Discussion. The present availability of analgesic agents reflects our shortcomings for the relief of patients with mild and moderate severities of pain. The potent analgesic drugs are reserved for severe pain usually in patients who are bedridden. Their use for ambulatory patients is not satisfactory because of the high incidence of untoward reactions with this group of patients. The mild analgesics of the salicylate and acetophenetidin types are usually insufficiently potent to affect many types of pain as seen in ambulatory patients. It has been the usual experience to prescribe codeine alone or in combination with various analgesic sedative mixtures for this type of patient. A high incidence of untoward reactions with chronic use of such preparations and the occurrence of tolerance with codeine have been the major drawbacks for satisfactory analgesic control. We feel that ethoheptazine more than satisfies our requirements for a moderately potent analgesic agent for the treatment of the ambulant patient. It is effective in the majority of etiologic conditions which might be encountered in practice. The combination with aspirin further enhances its usefulness. Certain patients might thus respond whereas the administration of either drug alone might be unsatisfactory. The occurrence of untoward reactions with ethoheptazine alone or in combination with aspirin is negligible and insignificant. Prolonged administration has proven to be safe. Within the limits of our study, we have been unable to demonstrate development of tolerance or physical dependence. Ethoheptazine satisfies to a high degree the need for a moderately potent analgesic administered orally.

Summary and Conclusions. 1. The effectiveness and safety of ethoheptazine, a new potent analgesic with a seven-membered cyclic ring structure, were studied in 330 patients requiring analgesia for a wide variety of medical and surgical conditions. Two additional groups of patients, totaling 127, were given ethoheptazine with aspirin.

2. Satisfactory analgesia regardless of etiology of painful state was achieved in 73% of ambulatory patients.

3. Sixty-two per cent of hospitalized patients responded, but required a higher dosage.

4. Postpartum pain was satisfactorily controlled in 82% of the patients treated with ethoheptazine alone and in every instance treated with combined ethoheptazine and aspirin.

5. The occurrence of insignificant untoward reactions was noted as 4% for both ambulatory and hospitalized patients.

6. The combination of aspirin with ethoheptazine enhances the likelihood of achieving satisfactory analgesia.

7. Ethoheptazine administered orally is an effective and safe moderately potent analgesic.

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SUMMARIO IN INTERLINGUA

Efficacia Analgesic de Ethoheptazina in Administration Oral a Humanos

1. Le efficacia e le grado de innocuitate de ethoheptazina, un nove e potente analgesico con un structura cyclic a septe membros, esseva studiate in 330 patientes qui requireva analgesia in consequentia de un grande varietate de conditiones medical e chirurgic. Duo gruppos additional de patientes, insimul 127, recipeva ethoheptazina con aspirina.

2. Analgesia satisfactori, sin reguardo al etiologia del stato dolorose, esseva effectuate in 73% del patientes ambulante.

3. Sexanta-duo pro cento del patientes hospitalisate respondeva, sed illes requireva plus alte doses.

4. Dolores post parto esseva subjugate satisfactorimente in 82% del patientes tractate con ethoheptazina sol e in 100% del casos tractate con ethoheptazina in combination con aspirina.

5. Le occurrentia de non significative reactiones adverse habeva un incidentia de 4% inter le patientes tanto ambulante como etiam hospitalisate.

6. Le combination de aspirina con ethoheptazina augmenta le probabilitate del effectuation de analgesia satisfactori.

7. Ethoheptazina in administration oral es un efficace e innocue analgesico de moderate potentia.

STUDIES ON PAIN: THE RELATION BETWEEN CUTANEOUS VASODILATATION, PAIN THRESHOLD AND SPONTANEOUS ITCHING AND PAIN

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Observation of patients with chronically itching skin lesions falling into the general group of "eczema" showed that itching was almost always increased at times of cutaneous vasodilatation (Graham and Wolff[7]). Pain threshold has been observed to be lowered in an area of itching skin (Graham, Goodell and Wolff[6]). It has also been observed that during vasodilatation linked with stress, mucous membranes of the nose (Holmes *et al.*[13]), stomach (Wolf and Wolff[19]), colon (Grace, Wolf and Wolff[5]), bladder (Straub, Ripley and Wolf[17]), and vagina (Duncan and Taylor[4]), pain can be elicited with less intensity of stimulation than when vasodilatation is not evident. Tingling and itching often accompany facial blushing associated with embarrassment. Also at such times, in postherpetic scars of the forehead, burning and tingling may be initiated or worsened. It therefore became of interest to investigate the relation of peripheral vasodilatation to changes in skin sensitivity.

It would have been desirable to measure variations in the cutaneous threshold for itching, but efforts to find a method of inducing itching without pain in a way which permitted expression of the stimulus intensity in physical units were unsuccessful. However, much evidence indicates that sensations of itching and of pain implicate the same neural apparatus. Pain is felt when noxious stimulation of the skin is sufficiently strong; itching occurs when the stimulation is less (Graham, Goodell and Wolff[6]). Bishop[3] also noted this when a single nerve ending was stimulated.

Therefore, measurements of changes in the cutaneous threshold for pricking pain during experimentally induced vasodilatation were undertaken. It was expected that if there were a lowering of the threshold during vasodilatation, then pain sensitivity would be increased.

A complete description of events in the cutaneous circulation would include discussion of both the arterioles and the "minute vessels" (capillaries and venules). The former influence chiefly the skin temperature, the latter, chiefly skin color. For practical reasons, the skin temperature, which reflects primarily arteriolar function, was the only measure of cutaneous vascular

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activity employed in the present experiments (Lewis[14]).

Subjects and Procedure. The subjects in the investigation were the three authors, all healthy adults without skin disease. One other healthy adult male was used for two experiments.

The skin temperature, measured by a Hardy radiometer (Hardy and Soderstrom[9]) was followed as an index of the state of the arterioles. Changes in pain sensitivity were followed in some of the experiments by the thermal radiation method of Hardy, Wolff, and Goodell[8,10] which measures the threshold in terms of the amount of radiant heat (mcals./sec./cm.^{2}) required to elicit pricking pain. This introduced the possibility that apparent decreases in threshold were due, not to a true alteration in the sensitivity of pain endings in the skin, but to the fact that less heat would have to be added from the heat source when the skin was already warm as a result of vasodilatation (Hardy, Goodell and Wolff[8]). Therefore the levels of skin temperature reached with the intensities of thermal stimuli just eliciting pain were calculated. The formula $T_s = T_i + 0.035Q\sqrt{t}$* given by Lipkin, Bailey and Hardy[15] was used. Also, in other instances the less precise and convenient von Frey hair[18] was employed in order to obtain thresholds for mechanical stimulation as well.

When the von Frey hair was used, the threshold was ascertained by Fechner's "method of right and wrong cases"[20]. The pressure exerted by the hair is a function of its length, which is adjustable. The pressures exerted at different lengths were directly determined on a laboratory balance, and are expressed in grams. In the determination, the percentage of contacts perceived by the subject as painful at different hair-lengths was obtained, and the threshold calculated by interpolation. In five experiments, using immersion of the feet in hot water as a means of inducing vasodilatation elsewhere in the skin, the length of the von Frey hair was held constant and increase in the frequency of recognizing pain sensation was used as the measure of lowered pain threshold.

The temperature of the room used varied between 23° C. and 27° C., but was relatively constant in any single experiment, not changing more than 1° C.

The plan of the experiments in general consisted, first, of obtaining control measurements of skin temperature and pain threshold both by thermal and by mechanical stimulation. After these had been found to be stable over a period of at least 10 minutes, procedures designed to produce arteriolar dilatation were employed. Skin temperature and pain threshold were ascertained at intervals of 2 to 10 minutes, the frequency being determined by the rate at which changes were occurring. The skin temperature was always the first of each pair of measurements. It was found that no error was introduced by measuring the temperature and pain threshold at the same site on the skin, since sufficient time elapsed after the threshold testing to permit dissipation of the heat introduced by the apparatus before the next temperature measurement was made. This conclusion was confirmed by comparing temperature readings at corresponding sites on the two sides of the body.

In most experiments, measurements were made during the phase of development of vasodilatation, at its peak and thereafter until a return toward control levels of both pain threshold and skin temperature was defined. Vasodilatation was induced as follows:

1) Reflex vasodilatation was induced by immersion of the feet and legs in hot water, with consequent vasodilatation in other regions. (In 5 of the 9 immersion experiments, hot liquid was ingested to further vasodilatation.)

Aluminum chloride was applied to the small skin areas to be tested in order to prevent sweating when vasodilatation was induced by immersion of the feet and legs in hot water. This substance had in itself no effect on either skin or pain threshold.

2) The administration of 100 to 250 mg. of nicotinic acid orally, or 40 mg. intravenously induced a generalized vasodilatation, more in some areas than in others, most conspicuously on the face and the back of the trunk.

3) The intravenous injection of 35 to 50 mg. of Priscoline (benzazoline hydrochloride) induced extremely rapid and short lived generalized vasodilatation.

4) The subcutaneous injection of 6 mg. of Mecholyl (acetyl-beta-methylcholine) induced a generalized vasodilatation, more in some areas than in others, most conspicuously

*In which T_s = skin temperature (°C.) at pain threshold
T_i = skin temperature (°C.) at start of irradiation
Q = intensity of radiation in mc./sec./cm.^{2}
t = duration of exposure in seconds
0.035 = constant determined by $K_\rho C$ (Thermal conductivity)

on the face and the back of the trunk.

Additional experiments were performed in which the skin was heated by a focussed gentle stream of hot air, without inducing the reddening of the skin indicative of arteriolar vasodilatation. These were undertaken to ascertain whether the changes in pain threshold resulting solely from rises in skin temperature would differ from the changes in sensitivity measured during vasodilatation. The treating of the skin by the hot air resulted in skin temperature elevations comparable to those associated with vasodilatation. In these experiments the gentle stream of hot air from a small electric hair dryer was used. The dryer was held at a distance from the skin such that there was no element of pain or pressure in the sensation resulting from playing the hot air on it for 2 to 3 minutes. The skin temperature was measured, just before, and immediately after, pain threshold was ascertained to make sure that the temperature had not changed significantly while the threshold value was obtained. It was found that the temperature never varied more than 0.2° C. and usually only 0.1°C. The two sides of the upper back and the cheeks were used as test areas.

COMMENT. In experiments of this type there is a drawback in the use of subjects who know what the purposes of the research are, in that they may be unwittingly influenced in reporting the presence or absence of pain by their knowledge of the expected results. Such an objection could be partially met if they were kept in ignorance of the particular experimental condition prevailing, but unfortunately, the presence of cutaneous vasodilatation is obvious to the person in whom it takes place. (Subjects were not, of course, told what stimulus intensity was being used at any time.) On the other hand, in order to obtain reliable reports, the subjects must have a certain amount of training and also be well-motivated, since the experiments are often tedious and the subjects are sometimes uncomfortable. The obvious difficulty in finding such persons led us to choose what seemed to be the lesser of the two evils, and (with the exception of two experiments) use ourselves as subjects.

A more direct answer to the question of changes in pain threshold accompanying the cutaneous vasodilatation of patients with certain skin disorders might have been obtained by carrying out the appropriate measurements on such persons, both in the presence and absence of vasodilatation. The difficulties in training and motivation mentioned above made it seem wise to postpone such an extension of the study, which is now being undertaken by one of the authors.

Results. The data of representative experiments are presented in Figs. 1, 2, 3 and 4, and the data are summarized in Table 1. Included in the latter are mean thresholds in experimental and control periods for each of the types of experiments performed, under conditions of vasodilatation and nonvasodilatation, using both thermal and mechanical methods for ascertaining threshold. Change in the threshold during the experimental periods is expressed as a percentage of the control threshold. Significances of differences between control vs. experimental periods, that is, of vasodilatation vs. nonvasodilatation periods, were calculated. In addition the temperature of the skin at which threshold pain was elicited during the the control periods (nonvasodilatation) and vasodilatation, were calculated. It will be seen in Table 1 that in all cases associated with vasodilatation, except in the case of the 5 experiments using Priscoline administration, there was significant fall in pain threshold (the probability of such resulting from chance was less than 0.01). Likewise, the threshold fall during vasodilatation periods were (again, with the exception of the 5 Priscoline experiments) significantly greater than the fall during nonvasodilatation periods (that is, those in

TABLE 1.—PAIN THRESHOLDS DURING CONTROL (BEFORE SKIN TEMPERATURE RISE) AND EXPERIMENTAL (AFTER SKIN TEMPERATURE RISE) PERIODS, WITH AND WITHOUT VASODILATATION. THRESHOLDS WERE MEASURED BY THE THERMAL RADIATION METHOD EXPRESSED IN mc./sec./cm.² AND BY THE VON FREY HAIR, EXPRESSED IN GRAMS OF PRESSURE.

Procedures	*No. of Exps.*	*No. of Subjs.*	*Mean skin temp. rise ° C.*	*Mean Control Pain Thresholds on back or cheek*		*Mean Experimental Pain Thresholds on back or cheek*		*% Change in Pain Threshold*	*Significance*	*Mean Skin Temp. at Pain Threshold*		
				mc./sec./cm.²	*mg.*	*mc./sec./cm.²*	*mg.*			*Control*	*Experimental*	△
A. Vasodilatation reddening of the skin												
Nicotinic Acid												
Thermal	7	4	1.2°	191	—	156	—	−20	P = <.01	45.8°	43.1°	−2.7°
Mechanical	5	3	1.1°	—	3.3	—	1.7	−48	P = <.01	—	—	—
Mecholyl	3	3	1.0°	182	—	152	—	−17	P = <.01	44.6°	42.9°	−1.7°
Priscoline	5	2	0.7°	188	—	176	—	− 7	not sig.	45.8°	45.2°*	−0.6°
Feet in hot water	9	3	1.1°	182	—	154	—	−16	P = <.01	45.3°	42.9°	−2.4°
B. No apparent vasodilatation; no reddening of the skin noted.												
Hot Air Blower												
Thermal	18	4	1.3°	182	—	175	—	− 4	not sig.	44.7°	45.7°	+1.0°
Mechanical	4	2	1.3°	—	2.3	—	2.6	+13	not sig.	—	—	—

* See discussion.

which rise in skin temperature comparable to that which occurred with vasodilatation, was induced by hot air). (See Table 1.)

The lowest pain thresholds did not usually coincide with the point of highest skin temperature rise and in the case of Mecholyl, pain thresholds at times of maximal skin temperature were as high as those of the control period (see Fig. 1). Inspection of individual protocols revealed that, in fact, the lowest pain thresholds occurred when vasodilatation was developing, and before it had reached its maximum. (See Figs. 1, 2, 3 and 4.) Pain thresholds frequently returned toward control levels before there had been a drop in skin temperature. This was usually in association with evidence of edema. In every instance in the rising phase, the level of the skin temperature at pain threshold was lowered (as calculated by the formula mentioned above). (See Table 1.) In the experiments using Priscoline as a vasodilator, although the observed lowering of pain threshold and rise in skin temperature were not statistically significant, nevertheless, the critical level of skin temperature at pain threshold was lowered as much as 1.4° C. in 2 out of 5 experiments. (See discussion below.)

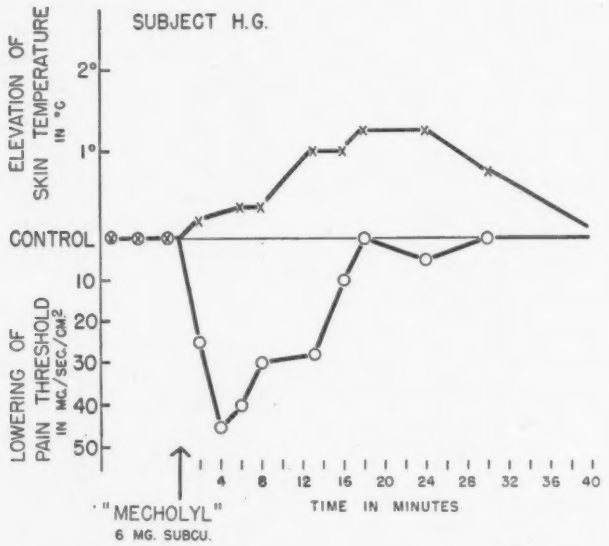

Fig. 1.—Relation of pain threshold lowering to vasodilatation as indicated by skin temperature rise, following injection of 6 mg. Mecholyl subcutaneously. Measurements of the skin temperature and pain threshold made on blackened areas of the cheeks. The x = skin temperature; the o = pain threshold.

During the development of vasodilatation and at the time of lowered pain threshold the subjects usually reported "spontaneous" itching, and in all experiments there was increased itching in response to mild mechanical stimulation, as from the application of the von Frey hair or from the clothing.

Discussion. The data as summarized in Table 1 show a close association between rising skin temperature and decrease in pain threshold in the case

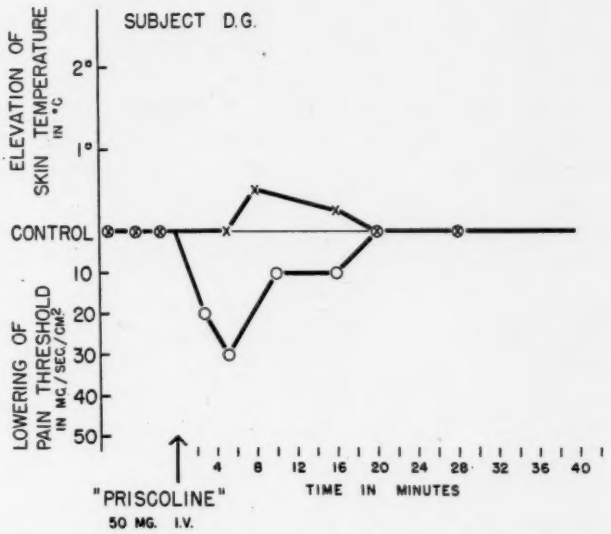

Fig. 2.—Relation of pain threshold lowering to vasodilatation as indicated by skin temperature rise following injection of 50 mg. Priscoline intravenously. Measurements of skin temperature and pain threshold were made on blackened areas of the cheeks. The x = skin temperature; the o = pain threshold.

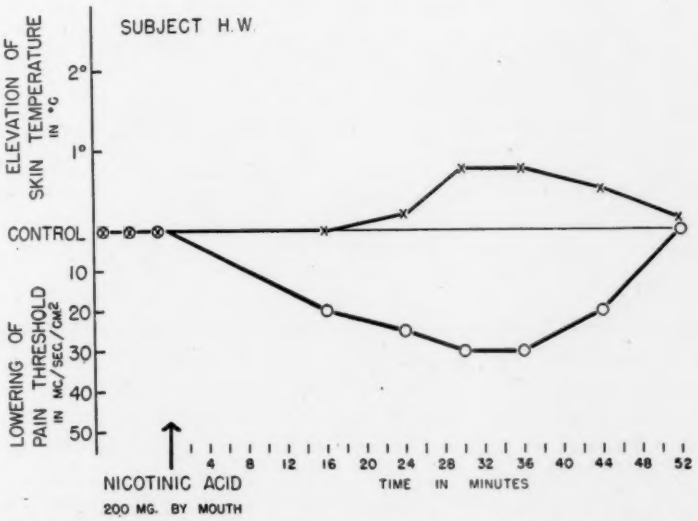

Fig. 3.—Relation of pain threshold lowering to vasodilatation as indicated by skin temperature rise, following ingestion of 200 mg. of nicotinic acid. Measurements of skin temperature and pain threshold were made on blackened areas of the back. The x = skin temperature; the o = pain threshold.

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of 3 of the 4 vasodilating methods employed. The skin temperature increases are indicative of increased cutaneous blood flow, following upon arteriolar dilatation. In the present experiments following ingestion or injection of vasodilator agents, reddening of the skin always occurred, indicating that there was an increased rate of blood flow and a concomitant dilatation of the minute vessels (Lewis[14]). Also, is associated with the described fall in pain threshold.

The probable explanation for the unpredictable threshold lowering observed after administration of Priscoline (significant lowering in only 2 out of 5 cases) is that vasodilatation occurred so rapidly and was so short lived that skin temperature and pain threshold measurements could not be made during the initial phase of vaso-

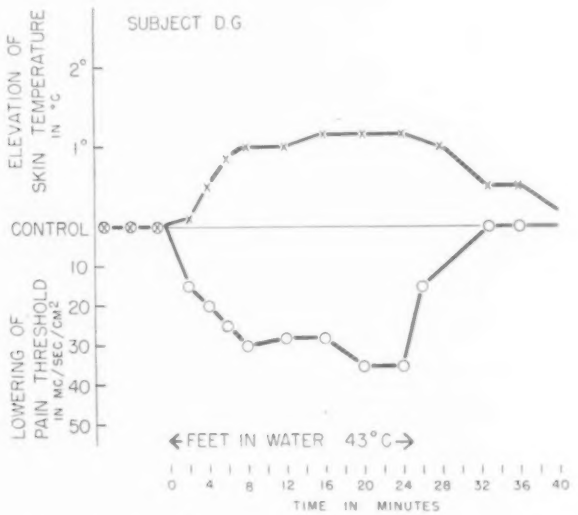

Fig. 4.—Relation of pain threshold lowering to vasodilatation as indicated by skin temperature rise, induced by immersion of the feet in hot water. Measurements of skin temperature and pain threshold were made on blackened areas of the back. The x = skin temperature; the o = pain threshold.

since the level of skin temperature at which pain is elicited by a thermal stimulus is lowered, it seems clear, therefore, that cutaneous vasodilatation is closely related to increase in the sensitivity of pain receptors in the skin.

In view of the fact that lowest pain thresholds were usually found on the ascending limb of the skin temperature curve, it seems probable that it is the initiation of vasodilatation rather than the persistence of vasodilatation that dilatation, linked in other experiments with more readily measurable lowering of the pain threshold.

Certain conjectures concerning the nature of this relation can be made. Presumably some factor linked with vasodilatation is essential to the threshold change. It is not clear exactly what components of the vascular change are the important ones, since the methods employed produced dilatation of both arterioles and minute vessels.

There are several ways in which vasodilatation might be involved in lowering the pain threshold. These include mechanical displacement of such nerve endings by edema fluid; stimulating effect of locally accumulated neurohumoral or chemical agents on the sensory nerve endings; warming of the nerve endings as the skin temperature rises, and possibly others.

An explanation of the pain threshold lowering effect in terms of warming of the nerve endings is not supported by the evidence, since warming of the skin by hot air in these experiments without producing vasodilatation actually raised the pain threshold when measured by the thermal method, and also when measured by the mechanical method (that is, with the von Frey hair). The slightly lowered thresholds measured with thermal radiation and expressed in (mc./sec./cm.^{2}) are compatible with the observations of Hardy, Wolff and Goodell[8] who showed that, in general, over a wide range of skin temperatures induced by raising or lowering environmental temperatures, a corresponding lowering and raising of pain thresholds (in mc./sec./cm.^{2}) occurred.

Additional evidence to support this inference that warming the skin is not the sole factor in lowering pain threshold comes from a series of observations made by Bilisoly, Goodell and Wolff[2] in this laboratory, demonstrating that pain threshold measured by the thermal method was significantly lowered in an area of reflex vasodilatation during the phase of spread of the flare of an axon reflex, even though the skin was cooled to its control level immediately before each measurement.

Schumacher[16] reported that the vasodilatation in the skin after ingestion of nicotinic acid was not followed by a decrease in pain threshold on the forehead. Since at that time there was no special interest in the temporal relation of vasodilatation and lowered pain threshold, Schumacher made his measurements for the most part after vasodilatation was well established, described as, "at maximum flush when there was tightness of the skin."

We observed that maximal lowering of threshold following nicotinic acid occurred during the initial period of flushing and not at the time of maximal flush when edema was evident. Furthermore, inspection of Schumacher's protocols shows that threshold lowering was recorded during the earlier phases of vasodilatation, while the flush was developing, and before its peak.

It is pertinent to distinguish the vasodilatation in the present experiments from that which Schumacher did report to be associated with a lowered pain threshold. By means of local trauma resulting from externally applied noxious stimulation, he produced inflammation, of which vasodilatation, is, of course, a part, and found the pain threshold lowered in the inflamed area. Lipkin, Bailey and Hardy[15] also measured pain thresholds during inflammation induced by ultraviolet light, and reported the critical level of skin temperature at pain threshold to be as low as 37° C. Our data indicate that the pain threshold in the skin is lowered by other than externally applied local noxious stimulation.

Nevertheless, perhaps the lowered pain threshold observed by Schumacher and by Lipkin, Bailey and Hardy with the vasodilatation of inflammation has features in common with the effect here described. As with vasodilatation induced by the chemical agents used, the reflex vasodilatation in the skin of the back, following immersion of the feet and legs in hot water, was accompanied by lowered pain threshold at

the site of the reflex dilatation in the back. Hence, it is unlikely that any direct local injuring effect of these particular chemical agents on blood vessel walls was solely responsible for the phenomena observed, that is, linking of vasodilatation and lowered pain threshold. As an explanation of this significant association, the thesis is suggested that regardless of the means used to induce the vasodilatation, during the initial phases thereof, a substance that is slightly noxious and that both injures the tissue and lowers the pain threshold, is released in the tissue. Lipkin, Bailey and Hardy note that lowering of the pain threshold may be related to the accumulation of protein breakdown products of tissue damage because the rate of catabolism exceeds the rate of anabolism. Since the postulated noxious agent is present in very minute amounts in the case of reflex vasodilatation, the pain threshold lowering effect is soon ended. In contrast, with burns from ultraviolet light, for example, the noxious agent continues to be formed in the damaged tissues for longer periods and hence, the pain threshold lowering effect persists for longer periods.

Such an explanation is in keeping with current views concerning the nature of the vasodilatation that is associated with chorda tympani stimulation. Here as a result of acetylcholine liberation (Babkin, Gibbs and Wolff[1], and Hilton and Lewis[12]), a proteolytic enzyme is secondarily released and slight tissue damage and vasodilatation ensue. One or more polypeptides may be the relevant agent. Also, Henriques[11], in studying the effects of thermal injury of the skin, has called attention to the denaturation of vital cellular proteins, to the alterations in metabolic equilibrium, to the increased permeability of cell walls and to the liquefaction of certain lipoid substances, all of which take place at the critical temperature of 45° C. He considered protein denaturation the process most likely to be relevant to the critical level of the threshold for tissue injury. This is significant in view of the fact that Hardy, Wolff and Goodell have demonstrated that 45° C. is also the critical level of skin temperature at which pricking pain is felt on thermal stimulation[10].

In the experiments described in this communication, there was greater lowering of the pain threshold in the skin during the initial phase of vasodilatation than would occur with the associated changes in skin temperature (Hardy, Goodell and Wolff[8]) and indeed, upon calculation it is revealed that the critical temperature for the stimulation of pain nerve endings was lowered. It is suggested that during vasodilatation there is an accumulation of one or more noxious agents, possibly the products of protein alteration in the tissue. In all events it is suggested that the first step in itching, and in some instances in spontaneous burning sensations occurring with a host of skin lesions, is vasodilatation and the accompanying fall in pain threshold. Hence, many weak stimuli, previously sub-threshold and giving rise neither to pain nor itching, are then intense enough to arouse itching.

Summary and Conclusions. 1) Thresholds for pain of pricking quality on the skin of the back during control periods were compared with those obtained during cutaneous vasodilatation induced by immersion of the legs in hot water (that is, reflex effects) and by administration of nicotinic acid, Mecholyl and Priscoline. In the study of the effects of nicotinic acid, and the reflex effects of immersion of the legs in hot water, both thermal and mechanical methods of estimating pain sensitivity were employed.

2) The pain threshold was lowered during the initial phases of vasodilata-

tion. At such times the subjects reported "increased itchiness" and "spontaneous" itching of the skin.

3) This effect was not mediated solely by the temperature rise accompanying vasodilatation, since the critical level of skin temperature at pain threshold was lowered, and since heating the skin with hot air to the temperature occurring with vasodilatation did not lower the pain threshold.

4) The lowest pain thresholds during induced vasodilatation were usually obtained as the skin temperature was rising, and they sometimes returned toward control levels during the period of maximum elevation of skin temperatures. This indicates that the lowered pain threshold of the skin was intimately associated with the initiation of vasodilatation rather than with the fully vasodilated state.

5) It is suggested that these observations explain the association of flushing of the skin and itching in patients with a host of skin disorders. Noxious stimulation barely at pain threshold intensity induces itching. It is therefore reasonable to suppose that many mild stimuli, ordinarily nonnoxious and not perceived, give rise to itching in skin in which the pain threshold is lowered in association with vasodilatation.

6) The proffered thesis to explain the association of cutaneous vasodilatation and lowered pain threshold implies that regardless of how induced, during the initial phase of vasodilatation there is liberated locally into the tissues an agent (or agents) that both injures tissue and lowers pain threshold. When the amount liberated is minute, as during the onset of reflex vasodilatation, the pain threshold lowering effect is slight and transient and short lived itching may be one effect. When the amount of agent liberated is greater and persists longer, as with inflammation after skin injury with heat, the vasodilatation and pain threshold lowering effect is also prolonged and spontaneous pain or itching may ensue. Such a mechanism might apply not only to the skin but also to a variety of surface, subsurface and deep disease processes.

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SUMMARIO IN INTERLINGUA

Studios in Re Dolor: Le Relation Inter Vasodilatation Cutanee, Limine de Dolor, e Prurito e Dolor Spontanee

1. Le limines de dolores de qualitate piccatori in le pelle del dorso durante periodos de controlo esseva comparate con le limines correspondente constatate durante vasodilatation cutanee inducite per immersion del gambas in aqua calide (*i.e.* effectos reflexe) e per le administration de acido nicotinic, Mecholyl, e Priscolina. In le studio del effectos de acido nicotinic e del effectos reflexe de immersion del gambas in aqua calide, le sensibilitate a dolor esseva estimate per le uso de methodos tanto thermic como etiam mechanic.

2. Le limine de dolor esseva abassate durante le phases initial del vasodilatation. A tal tempores le subjectos reportava un "augmentate pruritivitate" e un prurito "spontanee" del pelle.

3. Iste effecto non esseva mediate exclusivemente per le augmento del temperatura que accompania le vasodilatation, proque le nivello critic del temperatura cutanee al limine de dolor esseva abassate e proque le calefaction del pelle per medio de aere calide usque al temperatura occurrente con le vasodilatation non reduceva le limine de dolor.

4. Le plus basse limines de dolor durante vasodilatation inducite esseva usualmente obtenite quando le temperatura del pelle montava, e a vices illos retornava verso le nivellos de controlo durante le periodo del elevation maximal del temperaturas cutanee. Isto indica que le reducite limines de dolor cutanee esseva intimemente associate con le initiation del vasodilatation plus tosto que con le stato de vasodilatation complete.

5. Es suggerite que iste observationes explica le association de rubor cutanee con prurito in patientes con un grande varietate de disordines del pelle. Stimulation noxie, a pena al limine de intensitate dolorose, induce prurito. Per consequente il pare rationabile supponer que multe leve stimulos, ordinarimente non-noxie e non percipite, effectua prurito in un pelle in que le limine de dolor es abassate in association con vasodilatation.

6 Le these hic presentate pro explicar le association de vasodilatation cutanee con abassate limines de dolor insiste que durante le phase initial de vasodilatation, sin reguardo a como isto ha essite inducite, il occurre un liberation local a in le tessutos de un agente (o agentes) que ha le duple effecto de insultar le tessuto e de reducer le limine de dolor. Quando le quantitate del agente(s) liberate es multo parve, como al momento del declaration de vasodilatation reflexe, le effecto de reduction del limine de dolor es leve e transiente, prurito de breve duration es possibilemente le sol effecto percipite. Quando le quantitate del agente(s) liberate es plus grande e persiste plus longe, como in le caso de inflammation post vulneration del pelle per calor, le effecto de vasodilatation e de reduction del limine de dolor es etiam prolongate, e dolor e prurito spontanee pote resultar. Il es possibile que un mechanismo de iste genere functiona non solmente in le pelle sed etiam in un varietate de processos pathologic superficial, subsuperficial, e profunde.

NEEDLE BIOPSY OF THE PARIETAL PLEURA IN TUBERCULOSIS

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The definitive etiologic diagnosis in pleural effusion often is not made. Because pulmonary tuberculosis is a common sequel to pleural effusion in tuberculin positive patients, it has been axiomatic to consider idiopathic effusions in such individuals to be tuberculous until proven otherwise. This approach to the problem is justified by the fact that a majority of such cases are tuberculous and by the fact that tuberculosis is a disease whose treatment is both specific and highly successful.

In recent years biopsy of the parietal pleura by thoracotomy has obtained a definitive diagnosis in many cases that would otherwise have remained in the idiopathic group. However, this procedure is a surgical one and, therefore, possesses obvious objectionable features even though the operation is considered to be one of minor proportions relative to its value.

More recently DeFrancis, Klosk and Albano[1] and Heller, Kellow and Chomet[2] have described their results of biopsy of the parietal pleura with the Vim-Silverman needle. This procedure appears to be as fruitful as open biopsy and has the following advantages: (1) simplicity, (2) convenience, (3) innocuousness, and, above all, (4) repeatability. The tissue obtained, though small in amount, may even be cultured. Therefore, as Katz[3] has recommended, needle biopsy should be tried first and, if it does not yield a diagnosis, open biopsy may be undertaken. With this approach the incidence of idiopathic pleural effusion can be greatly decreased in favor of cases with a definitive diagnosis.

Needle biopsy has been used at this hospital during the past year in all kinds of cases with the technique described by DeFrancis, Klosk and Albano[1] and Heller, Kellow and Chomet[2]. It has become common practice in the hands of interns and residents. In cases of effusion due to neoplasm needle biopsy has been of relatively little value because cell block of the pleural fluid is usually diagnostic. However, in the diagnosis of tuberculous cases the procedure has much to offer, particularly since the etiology may be demonstrated within several days whereas cultures of fluid for tubercle bacilli, when positive, require weeks to confirm the diagnosis.

The purpose of this report is to summarize the results of needle biopsy in a series of patients treated as having tuberculous pleural effusion in order to estimate the value of the procedure.

Method and Material. The method of biopsy was that described by DeFrancis, Klosk and Albano[1]. Thoracentesis is done in the usual manner after local novocaine infiltration of the skin and intercostal tissues. A 19 gauge needle, attached to a syringe, is inserted while aspirating. When fluid is obtained the progress of the needle is stopped and a hemostat is clamped on the needle at the skin surface. The needle is then withdrawn and the distance between the hemostat and the point of the needle is a measure of the depth of the parietal pleura. This distance minus approximately 1 cm. is measured on a Vim-Silverman biopsy needle from the point and marked with an-

other hemostat. Thus when the Vim-Silverman needle is inserted, after nicking the skin at the site of thoracentesis with a scalpel blade, it can be inserted only up to the level of the hemostat and the point of the Vim-Silverman needle will lie approximately 1 cm. external to the parietal pleura. The inner split needle of the Vim-Silverman assembly is then inserted to its fullest depth, the entire assembly is then rotated 360 degrees and removed. A small fragment of tissue can usually be found within the split needle.

Several pieces of tissue are usually obtained by repeating the biopsy through the same skin puncture and inserting the Vim-Silverman needle at different angles.

The patients included in this series are limited to those that were treated as tuberculous and, therefore, included individuals in whom the diagnosis was confirmed in various ways or individuals who were tuberculin positive and no other etiology was established for the pleural effusion. One or more cultures of pleural fluid for tubercle bacilli were done in all cases.

Results. The results are presented graphically in Fig. 1. Twenty-two patients are included and 12 of these had needle biopsies in which typical caseating tubercles were seen. The remaining 10 showed nonspecific inflammatory reactions with fibrosis. In each of these two groups the diagnosis of tuberculosis was confirmed by other methods in 5 cases, for a total of 10 cases. However, one of those in the "tubercle"

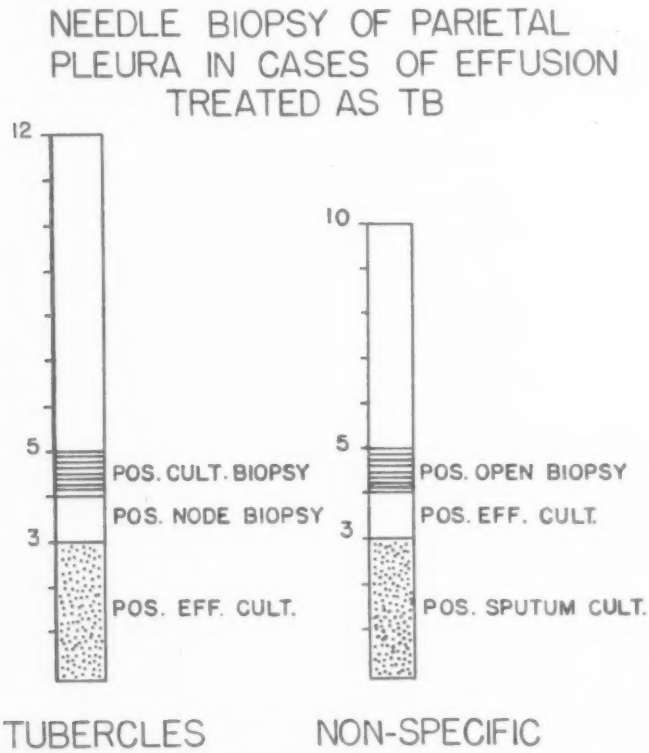

Fig. 1.—Bar graph of results of needle biopsy of the parietal pleura in 22 cases of pleural effusion treated as tuberculous. Those cases in which caseating tubercles were found are shown on the left while those in which the histologic findings were indicative of nonspecific inflammatory reaction are shown on the right. The cases in which the diagnosis of tuberculosis was confirmed by other means are indicated.

group was confirmed by positive culture of the biopsy material obtained with the needle. In one patient in the "nonspecific" group an open pleural biopsy was done and it showed caseating tubercles. Three patients in the latter group also had pulmonary tuberculosis and the diagnosis was established by positive sputum cultures. Culture of the pleural fluid was positive for tubercle bacilli in only 4 of the whole series.

Discussion. The results of needle biopsy in this series indicate that this is a valuable procedure in the etiologic diagnosis of tuberculous pleural effusion. It has been fruitful in approximately 60% of the cases whereas pleural fluid culture for tubercle bacilli was positive in less than 20%. Any method that will augment the diagnostic yield in "idiopathic" effusion is of increasing importance these days in view of the fact that tuberculosis in older men is more and more common. In this segment of the population the differential diagnosis between tuberculous effusion and malignant effusion is, therefore, of prime consideration. An early definitive diagnosis of tuberculosis as the cause of pleural effusion leads to earlier therapy and relieves some patients of the fear of cancer.

One may question the specificity of caseating tubercles since these lesions may be produced occasionally by other infectious agents. However, nontuberculous causes are uncommon enough that any error in diagnosis must be quite small in tuberculin positive patients.

Culture of the biopsy material was done in only 2 cases and one was positive for tubercle bacilli. Therefore, it is possible to use small bits of tissue for cultural purposes and it would probably be wise to incorporate this as a routine part of the procedure. Acid-fast stains of the tissue sections were done in a few instances but were negative. This also can be made a routine part of the procedure.

No untoward reactions were noted in this series or in any of the other numerous needle biopsies which have been done throughout the hospital during the past year. Heller, Kellow and Chomet noted a small hemothorax of no clinical significance in one of 22 biopsies done in 20 patients.

No preoperative medication was used in these patients since the procedure is of no greater consequence than thoracentesis.

If the tissue does not show a specific histologic picture on one occasion, it must not be assumed that tuberculosis has been excluded. In 2 cases the initial biopsy showed nonspecific chronic inflammatory reaction. When the biopsy was repeated caseating tubercles were obtained.

Thus it has been shown that all the advantages enumerated in the introduction are real and needle biopsy is a valuable tool to be added to the diagnostic armamentarium of the physician. It should be emphasized that needle biopsy does not exclude the need for bringing all diagnostic techniques to bear on a case of pleural effusion since biopsy may be negative when pleural fluid culture or open biopsy may confirm the etiologic diagnosis.

The frequency with which actual tubercles can be demonstrated in the parietal pleura lends support to the opinion that tuberculous pleural effusion is largely due to infection of the pleura rather than to allergic reaction.

Summary and Conclusions. Vim-Silverman needle biopsy of the parietal pleura in 22 cases of pleural effusion treated as tuberculous yielded tissue with caseating tubercles in 12 cases. This procedure was the single most rewarding diagnostic tool in this series.

Used in conjunction with other diagnostic methods, tuberculous etiology could be established in approximately three-fourths of the patients.

Needle biopsy has the advantages of simplicity, convenience, innocuousness, and repeatability.

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SUMMARIO IN INTERLINGUA

Biopsia a Agulia del Pleura Parietal in Tuberculose

Biopsias a agulia (de Vim-Silverman), effectuate in le pleura parietal in 22 casos de effusion pleural tractate como tuberculotic, produceva 12 specimens con tuberculos caseante. Iste manovra esseva le plus utile adjuta diagnostic individual in iste serie. In combination con altere methodos diagnostic, illo permitteva establir un etiologia tuberculotic in approximativemente tres quartos del casos.

Biopsias a agulia ha le avantages de simplicitate, innocuitate, e repetibilitate.

HISTOPLASMOSIS IN BROOKLYN

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and

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More than 50 years have passed since Darling described the first case of histoplasmosis. This observation has been followed by many investigative studies which have clearly defined the many different facets of this disease (Emmons[2], and Silverman *et al.*[16]). Da Rocha Lima insisted that *Histoplasma capsulatum* could not be a protozoon because it was Gram-negative. As early as 1912 he claimed that the microörganism was a yeast-like fungus. It was not until 1933 that de Monbreun was able to prove this contention by culturing the fungus from the blood and the spleen of a child. He then reproduced the disease in monkeys by inoculation of material from these cultures.

For more than 3 decades the disease caused by histoplasma was considered to be a great rarity and in 1940 only reports of 32 cases had been published. But in 1939 Esmond Long[8] anticipated a change when he stated in an editorial, "There is still room to doubt that all the lesions commonly diagnosed as calcified nodules of primary tuberculosis are really tuberculosis. Where calcifications are present in half the adolescent population it is pertinent to inquire if there could be any other cause than tuberculosis for the calcifications."

The answer to this inquiry was not long in coming. Six years later, studies in Tennessee by Christie and Peterson[1], showed correlation between the presence of pulmonary calcifications in tuberculin negative individuals and skin sensitivity to histoplasmin. The same year Palmer[12] reported similar findings, and it gradually became evident that subclinical histoplasmosis was an endemic disease which leaves in its wake widespread pulmonary calcifications and skin allergy.

This asymptomatic benign form with multiple pulmonary calcifications in tuberculin-negative individuals residing in the central states of North America* (Furcolow[5]) is the most common type of histoplasmosis. In addition, Schwartz *et al.*[15] report that in these endemic areas calcific lesions in the spleen are frequently seen. This leads to the conclusion that histoplasmosis, even in these latent cases, has at one time been disseminated by the blood stream to the spleen and, perhaps, other organs.

Apart from causing these clinically benign endemic cases, histoplasmosis also leads to acute and often dangerous manifestations. Parsons and Zarafonetis[13] and others (Mankiewkz, Blank and Rubin[9], and Peoples and Spence[14]) emphasized that fever, pneumonia, hepatomegaly, splenomegaly, lymphadenopathy, hypochromic anemia, leukopenia and albuminuria frequently occur in histoplasmosis. The excellent papers of Christie[1] clearly illustrate that acute histoplas-

*Kansas, Missouri, Illinois, Ohio, Kentucky, Texas, Louisiana, Arkansas, Oklahoma.

mosis in children can be an extremely dangerous malady.

It is well known that histoplasmosis occurs not only in the endemic areas mentioned above, but also, though less frequently, in other parts of the country. In New York State there are at least 2 small endemic areas which are located close to the Canadian border. Isolated cases have also been observed in other areas. Because of the extreme rarity of indigenous cases the diagnosis may not be suspected in the New York region, even if the patient has contracted the histoplasma infection elsewhere.

Three cases of this disease have recently been observed in the Brooklyn area and are the basis of this report. Each case demonstrates characteristic features of the disease and may serve to aid others in the recognition of hitherto unrecognized instances of histoplasmosis.

Case Reports CASE 1. In 1956, a 31-year-old white male was admitted to the hospital with the chief complaint of repeated attacks of nausea, vomiting, heartburn, and epigastric pain.

Past history was not contributory except that he had been stationed in army camps in Kentucky, Alabama and Tennessee from 1942–1946. He could not recall any serious or respiratory illness during that period.

Physical examination was essentially normal. Analysis of the urine was normal. Blood counts were normal except for an eosinophilia of 4 and 5%.

Roentgen studies revealed a duodenal ulcer. As an additional finding on the routine chest plate, multiple discrete, small, so-called submiliary pulmonary calcifications were seen.

Tuberculin skin test 1/1000 was negative. Histoplasmin 1/100 was markedly positive with vesiculation.

Cultures for fungi from gastric aspirations, bone marrow and buffy coat were all negative. Complement fixation tests with the yeast-like cell antigen of *H. capsulatum* were mildly positive.

COMMENT. Prior to the recognition of the benign form of pulmonary histoplasmosis leading to calcification, such Roentgen findings on a routine chest plate would have initiated a long search for the presence of a tuberculous infection. It is now realized that the negative tuberculin test, the positive histoplasmin skin test and this patient's army assignment to three states where histoplasmosis is endemic, all point to the diagnosis of "inactive" histoplasmosis of the lungs.

In the following case of pulmonary cavitation studied at this hospital, Hodgkin's disease was confused with histoplasmosis.

CASE 2. A 49-year-old salesman was admitted in 1953 because of fever and weakness. He stated that his illness had begun 7 weeks previously. He had been hospitalized in Montana where he was traveling at the time and remained at that hospital for 5 weeks, after which he was admitted to the Beth-El Hospital. While at the hospital in Montana his temperature ranged as high as 102° to 104° with sweating and shaking chills. A node was then removed from the left axilla and the patient stated that he was told he had Hodgkin's disease. He also complained of bleeding from the right ear and the nose. Weight loss was 17 pounds in the preceding 5 weeks.

The patient was born in Russia and had traveled extensively in the United States. Other symptoms and family history were not contributory.

On examination he appeared pale and chronically ill but not in acute distress. The blood pressure was 100/80, pulse 108, respirations 24, and the temperature 101°. The skin and conjunctivae were pale and without icterus, rash or cyanosis. The eyes, ears, nose and throat were normal. In the neck there were a few small discrete posterior cervical nodes. The thyroid gland was not enlarged; the trachea was in the midline. There was no other lymphadenopathy except for some small lymph nodes in the inguinal region.

Crepitant rales were present in the right base and axilla, but otherwise the lungs were clear to percussion and auscultation. The heart was not enlarged; a sinus tachycardia was present and a soft systolic murmur was found in the pulmonic area.

The liver was enlarged, soft and nontender and palpable 4 fingers below the costal

margin. The spleen was enlarged to 2 fingers below the costal margin. The remainder of the abdominal examination was normal as were the genitalia. Rectal examination was normal. The extremities were normal and there was neither clubbing nor edema. The neurological examination revealed normal findings.

The admission blood count showed a hemoglobin of 11 gm. per 100 ml., red blood cells numbered 3.8 million per c.mm., and the leukocytes 4,100 per c.mm., with a non-remarkable differential. Platelets were reduced to 80,000 per c.mm. The findings remained about the same with persistent leukopenia but the hemoglobin and platelets rose in the next few weeks. Urinalysis was negative except for occasional slight albuminuria. Specific gravity was as high as 1.021. The fasting blood sugar was 92 mg. per 100 ml., blood urea nitrogen 15 mg. per 100 ml., total protein was 6.6 gm.%, with albumin 4.2 gm.% and globulin 2.4 gm.%. The alkaline phosphatase was 11.6 units (King-Armstrong), the bilirubin 0.7 mg. per 100 ml., cholesterol 214 mg. per 100 ml., and cephalin flocculation was 3+ and 4+. The spinal fluid examination was normal. Repeated blood, urine, sputum and stool cultures were negative. While the total serum proteins remained about the same, later in the hospital course there was a tendency toward hypoalbuminemia.

Roentgen studies were performed with the following result: the heart was normal with aortic configuration. A circumscribed, soft, nodular infiltration was described in the right upper lung field near the first and second anterior ribs measuring 3 × 2 cm. Spine and pelvis were normal; an intravenous pyelogram was normal. The gastrointestinal Roentgen-ray examination was normal but an enlarged liver and spleen could be seen. An electrocardiogram was normal.

Initially various antibiotics were administered, but the temperature elevation continued, the anemia, leukopenia and thrombocytopenia persisted. Bone marrow studies revealed a cell-poor marrow with numerous nucleated red cells. The bleeding time was one minute and coagulation time was 4 minutes. The clot retracted partially after 8 hours. Fragility of the red cells was normal. The bromsulfonphthalein test showed 1.9% retention in 45 minutes. A tuberculin patch test was positive but the Mantoux test 1:100 was negative. The coccidioidin skin test also was negative. The sputa and gastric washings continued to be negative for acid-fast bacilli. Histoplasmin skin test was positive and the complement fixation test for histoplasmosis was weakly positive with the extract antigen of the yeast-like cells and a slight reaction with the yeast-like cell antigen of *H. capsulatum*. Repeat studies of the bone marrow showed a generalized depression of all elements. One bone marrow culture made at the Beth-El Hospital grew *Histoplasma capsulatum*. However, repeat bone marrow and blood cultures made both at the New York State laboratories and at the Beth-El Hospital were constantly negative. After 2 months the enlargement of the liver and spleen remained unchanged. The chest lesion, however, was progressive and roentgenograms revealed a clear radiolucent area in the upper outer aspect of the previously described infiltration in the right upper lung field, highly suspicious of cavitation.

The patient continued to run a downhill course with marked asthenia and fever. Since all confirmatory cultures had remained negative, steroid therapy was initiated. This treatment was chosen because it seemed possible that this patient was suffering from an atypical Hodgkin's disease and a secondary infection with *Histoplasma capsulatum*. The possible unfavorable influence upon the fungus infection was carefully weighed. Initially an adequate response was obtained, the temperature came down to normal, and the patient felt improved. The platelet and white blood count approached normal. After 3 months the liver and spleen were barely palpable and the lesion in the chest showed considerable resolution.

However, one month later the spleen and liver were again palpable, a low grade fever was present and icteric discoloration of the skin and mucous membranes became discernible. Liver biopsy showed normal liver cells with fibrous tissue. At this time the original lymph node biopsy performed in Montana was reviewed but a definitive opinion could not be reached. Since the favorable influence of the steroids apparently was transient, a course of nitrogen mustard injections was given. This was followed by a period of steroid therapy and subsequently by a second course of nitrogen mustard. Only then did the patient become afebrile, the jaundice cleared and the liver and spleen again became smaller. The lesion in the chest which had reappeared became smaller and the patient was discharged to a convalescent home.

The patient felt well for only 4 to 5 days when the fever returned accompanied by weakness and vomiting. The patient was readmitted 10 days following discharge. Examination now revealed intense jaundice, tem-

perature of 103°, hepatosplenomegaly, and ascites. The urine was positive for bile and urobilin. The blood urea nitrogen was 13 mg. per 100 ml., total protein 5.5 gm.%, with albumin 2.6 gm.%, and globulin 2.9 gm.%. The bilirubin was 4.1 mg. per 100 ml. direct and 10.8 mg. per 100 ml. in total. Alkaline phosphatase was 11.2 units (King-Armstrong), cephalin flocculation was 4+, and thymol turbidity 17. Bone marrow and blood cultures were sterile. The hemoglobin was 12 gm. per 100 ml., and the leukocytes numbered 6,100 per c.mm. with a normal differential. The sedimentation rate was 12 mm. per hr. Chest roentgenogram was unchanged.

Right-sided pleuritic pain developed but no effusion could be demonstrated. The downhill course continued and despite antibiotics, ACTH, and blood transfusions the jaundice and temperature remained unchanged. The patient died 7 months after admission.

Necropsy report: A chronically ill white male with icterus of sclerae and skin. No lymph nodes were palpable. The oropharynx and nasopharynx were filled with blood.

There were adhesions in the pleural cavity. The upper and middle lobes of the right lung contained diffuse areas of granular infiltration. At the right upper lobe a cavity 2½ cm. in diameter was filled with blood.

In the peritoneal cavity 700 ml. of dark yellow clear fluid was present. The spleen weighed 515 gm. and had a granular surface with focal grayish white granulations. The kidneys had a combined weight of 175 gm. with granular areas that exuded a milky white fluid.

The liver weighed 1,750 gm. and had a granular surface. On cut sections focal grayish white granulations were seen.

Large gray-white aortic glands were found.

Microscopic examination: The lungs showed moderately advanced fibrosis with areas of extensive infiltration of lymphocytes and mononuclear cells. Intracellular and extracellular histoplasma bodies were present. Coagulation necrosis was noted in the wall of the cavity. The liver showed periportal fibrosis and bile duct proliferation with lymphocytic infiltration. The spleen was moderately congested. The kidney showed necrosis of the renal tubules and glomeruli associated with hyperemia and infiltration of lymphocytes, mononuclears and occasional polymorphonuclears. The adrenal glands were free of disease.

Pathological diagnosis: Histoplasmosis of the lungs, lymph nodes and kidneys. Cavity of the lung (histoplasmosis) with ulceration of blood vessels and massive pulmonary hemorrhage. Portal cirrhosis and icterus.

COMMENT. Certain febrile forms of Hodgkin's disease can be confused with histoplasmosis and in addition the combination of Hodgkin's disease with histoplasmosis has been repeatedly reported. Only recently Nelson, Goodman and Oster[11] have emphasized this association. They describe 2 additional cases and review 23 cases previously presented in the literature.

In our patient one positive histoplasmosis culture had been found, but repeated cultures always remained negative. Since no effective treatment for histoplasmosis is known it was decided to try and influence the possible Hodgkin's disease with corticosteroids and nitrogen mustard. This medication was administered with great trepidation because it was fully realized that a fungus infection might react unfavorably upon corticosteroid administration. In our patient, who, at necropsy was proved to suffer from histoplasmosis without a complicating Hodgkin's disease, cortisone exhibited, at least temporarily, a palliative effect. This result, at the time, seemed to favor the diagnosis of Hodgkin's disease.

This response to cortisone deserves mention. In a case reported by Michael and Vogel[10] cortisone also contributed to the clearing of the pulmonary lesions, but, as in our case, it was feared that it might ultimately affect the fungus infection unfavorably.

Hemorrhagic tendencies have occasionally been reported in disseminated histoplasmosis (Little[7]) but there are no known studies that clarify the etiology. Thrombocytopenia has been implicated but the defect is probably a complex one.

CASE 3. This 58-year-old white nursemaid was referred to the hospital in 1956 because of bilateral infiltrations found on a routine chest roentgenogram. The patient had no

respiratory symptoms. There was no history of chest pain, hemoptysis, expectoration, night sweats, fever, or dyspnea, nor were there any cardiovascular complaints.

She stated that she was born in New York State and had never traveled. From 1916 to 1926 she lived on a farm 75 miles North of New York City where she had extensive contact with farm animals and poultry. She also stated that for 8 years she had been drinking mineral oil daily for constipation.

On examination, the patient was a moderately obese woman in no apparent distress. Except for a slight dorsal kyphosis the remainder of the examination proved to be normal. The chest was clear to percussion and auscultation and neither cyanosis nor clubbing were present. The radiologist reported multiple small infiltrations in both lung fields, more dense in the right lower lung field and in the mid-left lung. The hilar shadows were accentuated and calcific shadows were seen in the right hilus and right apex.

Urinalysis was normal. The hemoglobin was 13 gm. per 100 ml., the white count was 9000 per c.mm. with a normal differential. The sedimentation rate was 42 mm. and all blood chemistries were normal. The tuberculin skin test was negative at 1:10,000 and 1:1000 and positive at 1:100. The histoplasmin skin test was markedly positive at 1:1000, following which the patient had a temperature of 102° for 48 hours. Repeated gastric aspirations were negative for acid-fast bacilli. Complement fixation tests for histoplasmosis with the yeast-like cell antigen of *H. capsulatum* and coccidioidal infection were negative. Scalenus lymph node biopsy revealed a normal node from which no fungi could be cultured.

COMMENT. The history of this patient emphasizes a highly interesting feature in the epidemiology of histoplasmosis. In 1949, Emmons[3] stated that the source of infection appeared to be a mold growing as a saprophyte in soil. Gradually the importance of this observation has become evident. In 13 smaller or larger epidemic outbreaks reviewed by Grayston and Furcolow[6] the patients with acute histoplasmosis had always been in close contact with silos, barns, abandoned buildings or caves in which birds had been nesting and where large amounts of dried avian droppings were present. It is now generally accepted that individuals who are working or playing in areas where bird droppings are plentiful are in danger of becoming infected with histoplasmosis.

In this connection the reports concerned with the frequency of the saprophytic occurrence of histoplasma, especially in the soil of chicken farms, must be mentioned (Zeidberg and Ajello[17]). Chickens are not the hosts of histoplasma and Emmons[4] has been unable to demonstrate the presence of this fungus in 21 chickens who were sick with large livers and spleens. The same author cultivated 1,151 specimens of soil from different areas situated within a radius of 75 miles of Washington, D.C. In 104 specimens the presence of *Histoplasma capsulatum* could be demonstrated. Of these 104 specimens 73 consisted of litter from chicken houses or soil adjacent to or under the edge of chicken houses.

In this saprophytic growth phase histoplasma produces the most resistant form, the airborne conidia, which then may be disseminated in the dust and cause infection in humans by inhalation. In children, intestinal lesions are frequently found which indicates that in this age group the alimentary tract is also an important port of entry.

Discussion. Criteria for the diagnosis of this disease vary from one geographic area to another. If possible, a positive histoplasma culture should always be obtained. However, the difficulties which may be encountered are well illustrated by the results of the cultures obtained in our second patient. In the endemic zone of the United States the diagnosis is considered on the indirect evidence of a positive histoplasmin skin test, Roentgen findings in the chest (often calcific), and a negative tuberculin reaction (Silverman *et al.*[16]). In our area, many physicians are loathe

to accept the diagnosis without a positive culture. Nevertheless, when a patient shows the findings mentioned and has remained for a considerable time in an endemic area the diagnosis of histoplasmosis should be seriously considered.

Summary. Three cases of histoplasmosis observed in a Brooklyn hospital are reported.

Two cases were asymptomatic but revealed widespread pulmonary calcifications, negative tuberculin tests and positive histoplasmin tests. One of these patients had resided for 4 years in an endemic area, the other patient had had close contact with a poultry farm in upper New York State.

The third patient had fever of unknown origin, hepatosplenomegaly and pulmonary cavitation. One positive histoplasma culture had been obtained during life. At necropsy widespread histoplasmosis was found. A coexistent Hodgkin's disease, which had been suspected during life, was not present.

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SUMMARIO IN INTERLINGUA

Histoplasmosis in Brooklyn

Es reportate tres casos de histoplasmosis observate in un hospital de Brooklyn. Duo casos esseva asymptomatic sed revelava extense calcificationes pulmonar, negative tests de tuberculina, e positive tests de histoplasmina. Un del patientes habeva essite domiciliate in un area endemic durante un periodo de quatro annos. Le secunde habeva habite intime contactos con un ferma de aves domestic in un region rural del stato de New York.

Le tertie patiente habeva febre de origine non recognoscite, hepatosplenomegalia, e cavitation pulmonar. Un positive cultura histoplasmatic habeva essite obtenite durante le vita del patiente. Le necropsia revelava extense histoplasmosis. Coexistentia de morbo de Hodgkin, suspicite durante le vita esseva disprovate.

THE ADRENOGENITAL SYNDROME "VIRILIZING TYPE" IN AN ADULT MALE: A CASE REPORT

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Clinical manifestations of the virilizing syndrome depend upon the sex of the affected individual and age of onset. In a genetic female, excess androgen leads to female pseudohermaphrodism, the exact anatomic abnormalities depending upon whether the disorder developed *in utero*, after birth but before adolescence, or after full somatic growth and development have been achieved. The male child demonstrates an enlarged penis and other male secondary sexual characteristics but with small prepubertal testicles, indicating an extratesticular source of androgen. To our knowledge, the virilizing syndrome has never been reported in an adult male.

Case Report. G.H., a 36-year-old unmarried man complained of impotence and fatigue of 2 years' duration; the history was otherwise irrelevant. Physical examination was unrevealing excepting for testicles which were small-normal in size. Hair distribution was of masculine type including the abdomen, chest, arms, shoulders and legs, and there was moderate balding of the head. The clinical impression from the history and physical examination was, "no endocrine disease," and it was thought that the problem was essentially one of psychological impotence and fatigue. The results of several of the original studies (December 17, 1954) were, therefore, unexpected (see Table 1).

A blood count, urinalysis, glucose tolerance test, sedimentation rate, serum protein-bound iodine and cholesterol were normal. A testicular biopsy was performed and histologic sections were examined by 3 different pathologists in addition to the author. The consensus was that the sections were normal, excepting for some impairment in spermatozoal maturation.

The patient was given 5 mg. of prednisone 4 times a day for a period of 3 months, during which he reported improvement in strength but no change in libido. The dose of prednisone was reduced to 5 mg. 2 times a day, and the seminal fluid and urinary hormonal components were re-examined at intervals of 3 months. During this time the patient reported continued improvement in strength and increase in sexual urge.

Discussion. The increased levels of urinary total neutral 17-ketosteroids in control specimens (33.3 and 36.8 mg./24 hrs.), the slightly elevated urinary corticoids (367 and 454 mcg./24 hrs.), together with low or absent gonadotropins, low spermatozoal counts with deficient motility, and impairment of spermatogenic maturation noted in the testicular biopsy are consistent with adrenocortical hyperfunction and secondary gonadotropic insufficiency. The disproportionate increase in androgenic over corticoid elements and marked elevation of $C_{19}O_2$ components suggest the diagnosis of virilizing rather than Cushing's syndrome, and their reduction incident to prednisone therapy implies hyperplasia rather than tumor. The increase in $C_{19}O_2$ 17-ketosteroids

TABLE 1.—SEMINAL FLUID AND URINARY HORMONE STUDIES BEFORE AND AFTER PREDNISONE THERAPY.

Seminal Fluid	*Normal Values*	*Control Studies*			*Prednisone/mg./day**				*No Therapy*		*(Months)*
					20	*10*	*10*	*10*	*1*	*5*	*8*
Volume/ml.	2–5	3	3	3	3	3	5	3	3		3
Million/ml.	over 60	9	26	20	31	49	57	53	46		42
Active motile/%	over 75	25	20	20	55	55	40	35	35		50
Sluggish or nonmotile/%	under 25	75	80	80	45	45	60	65	65		50
Urine											
17-KS/mg./24-hr.	8–20	33.3	36.8		8.6	10	8.4	9.3	11.3	11.0	13.0
$C^{19}O^3$†	3.9–6.6‡		5.6		2.9						
$C^{19}O^2$†	5.5–6.9‡		20.1		7.1						
Etiocholanolone†	1.7§		6.2								
Androsterone†	0.6‡		6.6								
Dehydroepiandrosterone†	1.1§		0.2								
Allen%	under 5		3.9		0.3						
Cortic./mcg./24-hr.	80–300	367	454.0		844	393	815	390	170	230	
Gonad./m.u./24-hr.	13–52	0	0		37	108	62	34	214	62	
Est./m.u./24-hr.	13–26	13	0		44	27	27	13	67	13	

* Intervals of 3 months
† β-glucuronidase hydrolyzed, paper chromatographed
‡ 2 normal controls
§ 1 normal control

is due primarily (60%) to etiocholanolone and androsterone, excreted in approximately equal amounts which, according to Dorfman and Ungar[1] indicates the metabolism of Δ^4-androsterone-3, 17-dione derived from 17-OH Progesterone.

It is interesting that with prednisone suppression of the hyperfunctioning adrenal cortex to a normal level, presumably by depressing pituitary ACTH, urinary gonadotropins appear and rise to levels above normal for a male of this age. This may be prednisone effect alone (Sohval and Soffer[2]), but the persistence of normal 17-ketosteroids and estrogens, elevated gonadotropins and increase in spermatozoal count 5 months after the cessation of therapy suggests alteration of the fundamental metabolic abnormality.

Summary and Conclusions. A 36-year-old man is presented with impotence and fatigue and no abnormal physical findings. Urinary total neutral 17-ketosteroids were moderately elevated particularly the $C_{19}O_2$ fraction, and corticoids were slightly high. Etiocholanolone and androsterone excretion was increased and equal, suggesting that the precursor was 17-OH Progesterone. Spermatozoal counts were low with poor motility, and testicular biopsy revealed impairment of spermatozoal maturation. Prednisone administration resulted in amelioration of these abnormalities. It is suggested that the diagnosis is adrenogenital syndrome, "virilizing type."

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SUMMARIO IN INTERLINGUA

Le Syndrome Adrenogenital, Typo "Virilisante," in un Masculo Adulte: Reporto de un Caso

Es presentate le caso de un homine de 36 annos de etate, con impotentia e fatiga e nulle anormal constatationes physic. Le total 17-œtosteroides neutre del urina esseva moderatemente elevate, specialmente le fraction $C_{19}O_2$, e le corticoides esseva levemente alte. Le excretion de etiocholanolona e de androsterona esseva augmentate e equal, lo que indicava que le precursor esseva probabilemente 17-OH-progesterona. Le numeration spermatozoic esseva basse. Le motilitate del spermatozoos esseva reducite, e un biopsia testicular revelava un defective maturation spermatozoic. Le administration de prednisona resultava in le melioration de iste anormalitates. Es suggerite que le diagnose es syndrome adrenogenital, typo "virilisante."

SYRINGOBULBIA: REPORT OF AN UNUSUAL CASE

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Syndromes arising from lesions in the medulla are interesting for a number of reasons. Physicians most often consider this area to be a simple extension of the spinal cord, yet the functions are quite different. Disabling or invaliding lesions in the cervical cord may become rapidly fatal if they ascend into the medulla and the remainder of the cephalad-lying midbrain.

The prototype of acute infectious bulbar disease is acute bulbar poliomyelitis. This condition has become more frequently recognized at a time when it promises to be appearing less often. Among the chronic bulbar conditions, syringobulbia (medulla) and syringomyelia (cord) may present pictures more difficult to assay because of their slower progression and more varied facets. The developing syrinx (Greek: tube) may progress cephalad or caudad or both. A recent case of frequently complicated syringobulbia is reported:

Case Report. This 24-year-old white single female was admitted by ambulance to St. Michael's Hospital, Grand Forks, North Dakota, on October 22, 1954. She was referred by her local physician with a tentative diagnosis of bulbar poliomyelitis. The patient's illness had begun about 4 months before entry when she had experienced a transient attack of vertigo and incoordination associated with double vision. The symptoms cleared in a few days only to recur 3 months before entry, this time associated with dysphagia, hoarseness, and difficulty in phonation. There had been no known skeletal weakness or convulsions. The symptoms cleared in about one week.

A few days before admission she developed difficulty in swallowing with regurgitation of fluids through her nose and labored breathing. The day of entry the patient had delivered a macerated, approximately 4-month-old fetus in a neighboring hospital. Following this the patient's condition rapidly deteriorated, and her local physician felt that she would expire of respiratory paralysis. She was then transferred to our care.

Physical examination on admission revealed an acutely ill, white female who was unable to swallow even her own secretions. The respirations were labored, and the patient was cyanotic about the lips and finger tips, probably due to aspiration of pooled secretions in her pharynx. The patient was afebrile, her blood pressure was 104/70 mm. of Hg, and her pulse was 70 per minute and regular.

Neurological findings included a horizontal nystagmus as well as a constant vertical nystagmus. Diplopia was present as patient looked down and to the left. The gag reflex was absent with very little palatal function remaining. Large amounts of pooled secretions were noted in the relaxed pyriform fossa. There was an abductor paralysis of the vocal cords about 70% complete with a very weak adduction. At rest the cords assumed a cadaveric position. A good view of the anterior half of the vocal cords was not possible because of a dependent epiglottis that seemed

to be denervated on the left. The left vocal cord appeared to be more involved (weaker) than the right. The patient spoke with a distinct nasal quality to her voice. The seventh cranial nerve was intact as were the eleventh and twelfth. Deep reflexes were active and equal bilaterally, but an increased finger stretch reflex was noted on the left. No Babinski, Gordon, or Oppenheim reflexes were elicited. Coordination and sensation were apparently normal within the limits of testing available with this critically ill patient. The sphincters were functioning well.

Over both lung fields moist, sibilant rales were heard. Pelvic examination showed a normal multiparous lower genital tract. The cervix was patulous and from it exuded a thin bloody discharge. Rectal examination revealed the corpus uteri to be soft, anterior, and about the size of a 6 weeks' gestation.

LABORATORY EXAMINATIONS. The urine was negative except for a two plus albuminuria. Erythrocytes numbered 3,600,000;. hemoglobin was 11 gm. Leukocytes numbered 15,200 with a differential showing 90 polymorphonuclear cells including 3 stab cells, 7 lymphocytes, and 3 monocytes. Blood urea nitrogen was 8.5 mg. per 100 ml. Serology was negative. Spinal fluid examination showed an initial pressure of 140 mm. of H_2O, a final pressure of 100, and normal dynamics. The cell count showed 65 red blood cells; sugar was 39 mg. per 100 ml.; protein 16 mg. per 100 ml.; and colloidal gold curve 1122211100. Culture was negative.

A repeat lumbar puncture 5 days later showed a cell count of 1 white blood cell, a sugar of 41 mg. per 100 ml., a protein of 40 mg. per 100 ml., and again a negative culture.

Skull roentgenograms were negative as were roentgenograms of the cervical spine. Chest film showed an infiltration at the right lung base compatible with pneumonitis.

The patient's hospital course was one of gradual improvement over a 3-week period on supportive therapy only. She was discharged able to swallow quite adequately and with only minimal suggestion of the nasal type voice.

The patient was seen in follow-up one week later on November 26, 1954. At this time she was still able to swallow well with only slight regurgitation. No pharyngeal reflexes were present, and the soft palate moved only slightly on stimulation. A vertical nystagmus was still present. The left arm was weaker than the right, and although the legs were weak, gait and balance were well maintained.

MENTAL STATUS. During the succeeding 2 months the patient was seen at weekly intervals during which time she demonstrated considerable evidence of a chronic mental illness. A survey of her file from another physician's office (not the referring physician) revealed that she had written numerous obscene letters to him. She continued writing and mailing these notes to her present doctors following hospital admission. The notes demonstrated, among other things, an obsession with the use of obscene words. She was unable, however, to express any thoughts or even daily observations orally to her attending physicians, but expressed herself almost entirely by written communications. To the nurses and fellow patients she spoke slowly and briefly. She demonstrated the primary signs of a schizophrenic reaction with several accessory signs and symptoms, including auditory hallucinations to which she responded with loud laughter. She appeared to be concerned chiefly with sexual matters and indulged in various forms of sexual self-gratification including the coprolalia noted above.

On January 4, 1955, the patient was reexamined completely. She continued to show a slight nystagmus on lateral gaze, and the corneal reflexes were absent bilaterally. A suggestion of hypesthesia over the left face was noted as well as an increasing nasal quality to her voice. She was unable to swallow well and showed an absence of palatal movement, but no tongue fasciculations or facial weaknesses were noted. The left arm was weak and there was beginning atrophy of the left infra- and supraspinatus as well as of small muscles of the hand. The left scapula appeared winged. Biceps and deltoid weakness and atrophy were noted bilaterally, and it was felt there was an over-all diminution of the deep reflexes. The Hoffmann sign was now bilaterally present. There was a consistent hypesthesia of the left arm and shoulder girdle.

Repeat roentgenograms of the chest, spine, and skull were negative as was a spinogram.

Spinal fluid examination revealed no cells, protein 22 mg. per 100 ml., glucose 51 mg. per 100 ml., colloidal gold was now 5422100000. Fasting and 2-hour postprandial blood sugars were 76 mg. and 113 mg. per 100 ml. respectively. Blood and spinal fluid serologies were negative. Total serum protein was 6.9 gm. %. There was no Bence-Jones proteinuria detected. No heavy metals were found in the urine. Agglutinations against type 2 poliomyelitis virus were present in dilution of 1:1024.

Because of her progressive impairment of deglutition, the patient was returned home on tube feedings and supplementary vitamins.

Over the succeeding few months she was seen on several occasions. It was necessary to maintain her on tube feedings and a gastrostomy was considered. In general, however, she did not seem to be deteriorating, and her weight and general welfare seemed to be satisfactory.

In June, 1955, the patient was treated by another physician in the hospital for dysuria and frequency of urination. The laboratory findings were consistent with cystitis. She responded well to Gantrisin therapy and was discharged recovered.

The patient was not seen from July to October 1, 1955. On the latter date, despite now being 5 months' pregnant, she had lost 15 pounds. Again, too, she demonstrated decreased breath sounds and faint rales in both lung bases. Neurologically there was no marked change noted except an increased atrophy of the facial, scapular, humeral, and biceps muscles. Chest roentgenograms showed extensive infiltration in the lower half of both lung fields consistent with aspiration type pneumonia.

In addition the patient had developed a recurrence of cystitis with urinary frequency. On one occasion she received Dilaudid grain 1/64 and nearly expired during the next hour. Consequently she received only antibiotics and atropine during her last days. She became increasingly apprehensive, cyanotic, hypothermic, and in a panic state (November 13, 1955) pulled her gastric tube out and expired at 8:25 p.m.

POSTMORTEM EXAMINATION. Aside from the gravid uterus containing a fetus weighing 960 gm. and the presence of the patient's bilateral bronchopneumonia, pertinent findings were limited to the central nervous system.

Upon opening the cranial cavity there was revealed a 2.2 cm. ovoid gray-white to pink nodule arising from the dura 2 cm. to the right of the midsagittal line and over the anterior portion of the parietal lobe. Histologically it proved to be a psammomatous type of meningioma (Poser[5]).

The brain weighed 1420 gm. and did not appear unusual to gross inspection.

On sectioning, the brain stem revealed no gross abnormalities. At the junction of the spinal cord and medulla and extending downward to involve the cervical, thoracic, and upper lumbar segments of the cord was a large (up to 14 mm. in diameter) central cavity. Clear serous fluid filled this defect. There was a uniform thinning of the cord substance about the cavity.

Microscopic examination of the medulla as well as gross inspection of the stained sections showed two small slit-like cavities extending from the floor of the fourth ventricle anterolaterally at a 40° angle to the surface of the medulla. Gliosis and vascular proliferation were noted about the defects. There was less cavitation on the left than on the right. However, a line of gliosis and vascular proliferation occupied the same region as represented by the cavity on the right. The areas involved included the dorsal nucleus of the tenth nerve, the nucleus ambiguous, and the nucleus of the spinal accessory nerve as well as portions of the spinal nucleus of the fifth nerve.

Microscopic examination of the spinal cord at various levels revealed a continuous pattern of defect. Sections of the cord from the sacral and lower lumbar regions showed five tubular defects lined by a single layer of ependymal cells. In addition to these five distinct canals, there were clusters of ependymal cells not having a definite lumen. As the examination progressed cephalad into the upper lumbar segments, one observed the central canal as a distinct entity and nearby the abnormal cavity described above. The central canal persisted into the upper cervical regions where it was lost, only to reappear just inferior to the medulla. The large cavity persisted, retaining its ependymal lining and surrounding gliosis high into the cervical region. In the upper cervical segments the cavity was lined for the most part by glial tissue. In some zones a few ependymal cells were seen forming a lining or partial lining of the cavity. About the defect was extensive glial proliferation.

In several sections there was a slight fibrous thickening of the leptomeninges with a minimal infiltration by scattered monocytes and lymphocytes. There was a similar infiltration around a few blood vessels penetrating the substance of the cord. In the areas of glial proliferation there were scattered macrophages filled with old blood pigment and a small scattering of monocytes and lymphocytes. The ganglion cells of the anterior horn appeared prominent but not remarkable except for an apparent diminution in the number of such cells. Weil's stain failed to reveal specific zones or tracts of demyelinization in nerve trunks arising from the cord.

Discussion. The term syringomyelia was introduced in 1824 by Ollivier to

describe the formation of a cavity in the spinal cord. Classically the disease is considered to be due to imperfect closure of the neural tube, persistence of embryonic cell rests, and, frequently, cavity formation and liquefaction.

In 1883, Morvan discussed a patient who had developed an ascending hand infection from a whitlow on one of his fingers. The surgeon advised removal of the necrotic terminal phalanx and effected a quick incision to spare the patient's suffering. He was startled to find the procedure painless. He studied and reported several similar cases from which he described a condition of "analgesic weakness with whitlows of the upper extremities" (Netsky[4]).

Schlesinger[6] demonstrated cavities, also, as a result of traumatic hematomyelia, softening of inflammatory origin, malformations, tumors, and vascular changes. More recently other conditions have been shown to be associated with cavitation: the Arnold-Chiari malformation, platybasia (Chamberlain[3]), the Klippel-Feil syndrome, and herniation of intervertebral discs.

Two processes are essential to the formation of syringes in either the cord or the midbrain: (1) the glial proliferation, perhaps primary, and (2) the tendency toward cavity formation which may be secondary.

The clinical signs and symptoms of syringomyelia are characteristic of an expanding lesion in or near the central canal of the cord. Included are interruption of the pain and temperature fibers as they cross the midline and weakness due to destruction of the anterior horn cells. The disabilities seen in syringobulbia give the clinical picture of true bulbar palsy.

The case presented in this report demonstrates in part the wide variation possible from the classical descriptions of the disease and also the impact of complications upon the distorted cord and medulla.

Although this patient's history did not suggest an acute infectious process, her initial appearance made isolation advisable for 24 hours. The spinal fluid findings and a detailed history suggested a chronic disability. Neurological examination placed the process in the medulla and cervical cord.

For several months the patient did not present a picture of pain and temperature dissociation. She had early absence of corneal reflexes and only later demonstrated loss of sensation over the face. There appeared to be little evidence of facial weakness and at no time any suggestion of hypoglossal nerve involvement, although both cranial nerves are frequently involved in this disease. The seventh nerve when affected will give a peripheral type of facial weakness.

The dysphagia, dysphonia, and respiratory difficulties required constant care and vigilance. Baker's extensive work on management of bulbar poliomyelitis was consulted (Baker, Matzke and Brown[1,2]) and the parallel was easy to establish. Involvement of the tenth nerve produces weakness of the palate, pharynx, and vocal cords. The reflex spasm of the laryngeal muscles, paralysis of the vocal cords, aspiration of vomitus, and excessive secretions induce evidence of hypoxia with restlessness, anxiety, tachycardia, dyspnea, and cyanosis progressing to delirium and death in some cases.

This patient's paretic muscles of respiration were inadequate to sustain the additional burden of her two pregnancies and their relationship to the outcome cannot be overlooked. Her parents and her religion would not permit sterilization, and her parents, in addition, felt her mental status was not severe enough to indicate commitment.

This patient's exquisite sensitivity to analgesics was a grim reminder of the serious hazard inherent in the use of barbiturates and opiates in bulbar disease, not only in acute stages but even for many years later.

In addition to the weakness of the muscles of respiration, other problems arose from the proximity of the lesions to the respiratory and circulatory centers in the medulla. Despite an adequate airway and intact respiratory muscles, patients with involvement of the respiratory center may have irregularities in rhythm and depth of respiration. Hypoxia may appear with apprehension, increased pulse rate, and blood pressure changes. This patient may well have had such involvement as the terminal picture seemed to indicate.

In addition to the complications of pregnancy, pneumonia, and chronic mental illness, the problems resulting from syringomyelia in the lower neuraxis were considerable. The cystitis and occasional episodes of urinary retention most likely resulted from a neurogenic bladder dysfunction. She entered the hospital for the last time with a painful infection of her finger to contradict further the classic picture. It must be recalled that terminally all of her psychiatric disturbances became more severe, and she began to exhibit carphologia in the manner of the patient with pseudobulbar palsy or other chronic brain syndromes.

Summary. (1) A case of syringomyelia, extending from two cavities in the medulla to end in five distinct cavities in the sacral region, is here presented.

(2) The wide variations possible from the classical picture of these conditions are noted.

(3) Discussed also are the several complications present and their impact upon a damaged cord.

(4) A brief correlation between signs and symptoms and the pathological report is attempted.

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SUMMARIO IN INTERLINGUA

Syringobulbia: Reporto de Un Caso Inusual

1. Es presentate un caso de syringomyelia, partiente ab duo cavitates in le medulla e finiente in cinque distincte cavitates in le region sacral.

2. Es signalate le marcate variationes que es possibile in comparation con le tableau classic de iste conditiones.

3. Es etiam discutite le plure complicationes representate in iste caso e lor effecto super le defective medulla.

4. Es facite le tentativa de correlationar le signos e symptomas con le reporto pathologic.

ARTERIAL BLOOD OXYGENATION IN SICKLE CELL ANEMIA*

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Systemic arterial blood is often less than normally saturated with oxygen in sickle cell anemia (Leight *et al.*[11]). There are at least 2 possible explanations for this. One is that the arterial oxygen tension (pO_2) may be less than normal in sickle cell anemia. This seems not unlikely, since Ryan and Hickam[18] have described an increased alveolar-arterial oxygen tension gradient in other types of anemia. According to them the alveolar-arterial oxygen tension gradient rises as the blood hemoglobin level falls. Since sickle cell anemia is usually associated with rather low blood hemoglobin levels, a rather high alveolar-arterial oxygen tension gradient may be expected if this observation also holds true for sickle cell anemia. A second possibility is that the oxyhemoglobin dissociation curve of intracellular sickle hemoglobin may be different from that of normal intracellular hemoglobin, as suggested by the study of Becklake, Griffiths, McGregor, Goldman, and Schreve[3] in 4 patients with sickle cell anemia. The purpose of the present study is to confirm the occurrence of arterial blood oxygen unsaturation in sickle cell anemia and to determine to what degree it is due to an increased alveolar-arterial oxygen tension gradient, and to what degree it is due to abnormal uptake of oxygen by sickle hemoglobin.

Materials and Methods. The studies to be described were performed upon 10 Negroes, aged 15 to 40 years, with sickle cell anemia; upon 11 Negro control subjects without anemia, aged 28 to 53 years, and upon 8 subjects with anemia other than sickle cell anemia. In these subjects, ages were 15 to 58 years. Seven of these anemic patients were Negro and one was white. None of the sicklemia patients had received blood transfusion within 3 months at the time of study. The control subjects were convalescent patients from the surgical wards of Grady Memorial Hospital. Their diagnoses are given in Table 1. The diagnoses of the anemic patients are given in Table 3. None had clinical evidence of cardiac or pulmonary disease.

Arterial blood samples were obtained from an indwelling needle in the brachial artery. Fifteen minutes after insertion of an indwelling arterial needle, a 3-minute sample of expired air was collected in a Douglas bag. The expired air was analyzed for carbon dioxide and oxygen in the Scholander 0.5 ml. gas analyzer. Duplicate samples were required to check within 0.04%. Gas volume in the Douglas bag was measured in a wet-test meter. Simultaneously with the collection

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of expired air, three 15 ml. samples of arterial blood were collected, each over a one-minute period. Samples of arterial blood for oxygen and carbon dioxide tensions and content were collected in heparinized syringes and stored in ice over mercury. Arterial blood samples were analyzed for carbon dioxide and oxygen content in the Van Slyke manometric apparatus. Duplicates were required to check within 0.2 ml./100 ml. for oxygen and within 0.4 ml./100 ml. for oxygen tension analyses by the above method were performed upon blood equilibrated for 30 minutes at 37° C. with a gas of known oxygen tension in a tonometer. The oxygen tensions employed were from 23 to 109 mm. pO_2. The mean difference between observed and calculated tensions was 2.7 ± 1.3 (standard error) mm. pO_2, observed O_2 tension being less than actual tension. The difference was not significant statistically, $p>0.05$. Another technician analyzing blood

TABLE 1.—ARTERIAL BLOOD AND GAS DATA IN EIGHT NORMAL SUBJECTS BREATHING AMBIENT AIR

Patient, Age, Diagnosis	*Hb. gm./ 100 ml.*	*O_2 Saturation % Capacity*	*Arterial O_2 Tension mm.*	*Effective Alveolar pO_2 mm.*	*O_2 Alveolar-arterial Gradient mm.*	*Arterial pH*	*Arterial CO_2 Content ml/100 ml.*	*Arterial pCO_2 mm.*
1. W.T. 39/C/M; post-phlebitic leg ulcer	11.1	96.5	92	93	1	—	49.1	44
2. A.S. 29/C/M; abd. wound	11.9	96.7	101	97	−4	7.39	50.9	44
3. R.D. 34/C/M; esophageal stricture	12.5	98.6	91	95	4	7.36	50.0	45
4. W.H. 49/C/M; eczematoid dermatitis	10.9	96.1	88	99	11	7.30	42.0	42
5. N.H. 28/C/M; hernia	13.8	95.1	88	90	2	7.39	48.4	43
6. H.P. 30/C/M; foot fracture	13.4	93.7	84	98	14	7.41	45.2	38
7. H.M. 53/C/M; infectious diarrhea recovered	11.9	97.8	102	99	−3	7.38	42.6	38
8. C.J. 30/C/M; hernia	11.3	97.0	81	85.0	4	7.38	51.2	45
Mean ± S E	12.1	96.4 ± 0.54	91 ± 2.6	95±1.8	3.7±2.2	7.37±.01	47.4±1.3	42.4±1.0

carbon dioxide. Arterial blood samples were analyzed for oxygen tension (partial pressure) by the bubble equilibration method of Riley, Proemmel, and Franke[17] using 100 mm. capillaries fused to tuberculin syringes. Equilibrations were carried out in a constant temperature water bath maintaining 37° C. ± 0.2°. Reagents were equilibrated for 30 minutes with a gas mixture whose carbon dioxide and oxygen tensions, with the exception of the gas to be absorbed by that reagent, approximated that in the blood to be analyzed. Duplicate determinations were required to check within 6 mm. for pCO_2 and pO_2. No correction factor was used. In 14 instances, tensions in the patients with anemia other than sicklemia had no mean difference between tonometric and observed pO_2, in 20 instances, with pO_2 ranging from 58 to 108 mm. Hg, the standard error being 1.1 mm. partial pressure O_2. Arterial blood pH was determined in duplicate at room temperature, using the Cambridge glass electrode pH meter, and was corrected to 37° C. Arterial carbon dioxide tensions were calculated from arterial carbon dioxide content, arterial pH, and arterial blood oxygen capacity, according to the nomograms of Peters and Van Slyke[13]. These values were used for subsequent calculations, since the CO_2 tensions

determined by the bubble equilibration method were not satisfactory in our hands when checked with tonometer readings.

In 6 normal subjects and in 6 subjects with sickle cell anemia, the above determinations were repeated 10 minutes after the subject began breathing 15.6% oxygen in nitrogen. In some subjects, the previously described analyses were also made upon venous blood, with and without stagnation.

In 4 subjects with sickle cell anemia and in 3 normal subjects, blood equilibrations were done at varying oxygen tensions and at a carbon dioxide tension of 40 mm. partial pressure in glass tonometers of 263 to 391 ml. capacity, using a modification of the method described by Henderson[8]. Tonometers were filled with gas mixtures containing a pCO_2 of approximately 40 mm., and pO_2 of approximately 20, 40, and 60 mm. Hg. Eleven milliliters of heparinized blood were introduced, and equilibration for 30 minutes took place at 37° C. in a constant temperature water bath. Following equilibration, the tonometer was wrapped in a wet towel at 37° C., outside of which was placed a dry towel. The blood was quickly drawn off anaerobically into a sealed syringe and was analyzed for pH, and carbon dioxide and oxygen content. The pressure in the tonometer was measured with the Haldane apparatus, and the gas therein was analyzed for carbon dioxide and oxygen in the Scholander 0.5 ml. gas analyzer. Gas tensions in the tonometer were calculated from the following equation, modified from Henderson[8]:

$$pO_2 = [\%O_2]\,[(b+t)]\,\frac{(273+37°)}{(273+T)}\,\frac{(V+6)}{(V-11)} - 47]$$

Where pO_2 = Oxygen tension, mm.
b = Barometric pressure
t = Tonometer pressure
T = Room temperature, Centigrade
V = Volume of tonometer

The diagnosis of sickle cell anemia was confirmed by demonstration of the characteristic pattern for 100% sickle hemoglobin by paper electrophoresis.* In the control subjects, sickle cell anemia or sickle cell trait was excluded by the sodium bisulfite test (Daland and Castle[7]). The absence of sickle hemoglobin was demonstrated in the 8 anemic subjects without sicklemia by paper electrophoresis. Teleoroentgenograms of the chest were obtained in each patient with sickle cell anemia. Blood oxygen capacity in all subjects was determined by equilibration of 5 ml. of the patient's blood with room air in a stoppered Erlenmeyer flask for 15 minutes. Values of blood hemoglobin were determined by the oxygen capacity method of Van Slyke and Neill[13]. Vital capacities of 6 subjects with sickle cell anemia were measured with a Collins spirometer.

Effective alveolar oxygen tension for calculation of the alveolar-arterial oxygen tension gradient was determined by means of the alveolar equation, using arterial pCO_2 as an estimate of alveolar pCO_2 (Riley and Cournand[16]).

In one patient who had sickle cell anemia and congenital heart disease with atrial septal defect, a sample of pulmonary venous blood was obtained by the technique of right heart catheterization (Cournand and Ranges[6]) and was analyzed for oxygen content and saturation.

Results. The results are summarized in Tables 1, 2, 3, 4, 5. In the normal subjects, hemoglobins were 10.9 to 13.8 gm. per 100 ml. of blood (Table 1). In the sicklemia patients, hemoglobin determinations varied from 4.2 to 8.3 gm., and hematocrits were 12.5 to 26% (Table 2). In the other anemic patients, hemoglobins were from 2.9 to 8.3 gm. Mean hemoglobin level was 5.7 gm. per 100 ml. blood in the anemic patients without sicklemia and was 6.3 gm. per 100 ml. blood in the sicklemia patients. The difference in hemoglobin levels between sicklemic and nonsicklemic anemic patients was not significant, $p > 0.5$.

Arterial blood oxygen saturations of subjects breathing ambient air were 93.7 to 98.6% of capacity in the normal controls, with a mean of 96.5% ± 0.54 (standard error), Table 1. In the sicklemia patients, the arterial blood oxygen saturations while breathing ambient air were 80 to 92.6% of capacity (Table 2), showing no overlap with the normal. The mean in the sicklemic patients was 88.3 ± 1.42. The difference in mean saturations of

*We wish to thank Dr. Gerald Cooper, Communicable Disease Center Laboratory, Atlanta, Georgia, for performing these studies.

TABLE 2.—ARTERIAL BLOOD AND GAS DATA IN NINE SUBJECTS WITH SICKLE ANEMIA BREATHING AMBIENT AIR

	Hb. gm./ 100 ml.	*Hct*	*O_2 Saturation % Capacity*	*Arterial O_2 Tension*	*Effective Alveolar pO_2 mm.*	*O_2 Alveolar-arterial Gradient mm.*	*Arterial pH*	*Arterial CO_2 Cont. ml./100 ml.*	*Arterial pCO_2 mm.*	*Vital Cap. ml. & % of Predicted*
1. G. B. 39/C/M	4.2	12.5	84.0	67	98	31	7.40	49.9	40	2016 54%
2. B. B. 17/C/M	7.2	23.5	92.6	78	86	8	7.39	52.6	43	2360 55%
3. W. W. 23/C/M	5.8	20	80.0	61	99	38	7.38	46.3	37	—
4. B. H. 19/C/F	5.0	14.5	87.6	84	102	18	7.38	41.4	33	2000 46%
5. E. B. 26/C/F	5.5	18	91.0	91	113	22	7.39	37.8	28	2440 55%
6. H. L. 24/C/M	7.7	26	90.0	85	93	8	7.39	49.1	40	2360 56%
7. F. B. 40/C/F	6.0	21	86.3	76	108	32	7.38	36.2	29	—
8. D. Y. 25/C/F	7.0	24	92.4	80	106	26	7.37	38.0	31	2760 63%
9. E. M. 12/C/M	8.3	24.8	91.2	79	—	—	7.42	45.5	36	—
Mean±SE	—	—	88.3±1.4	78±2.9	101±2.9	22.9±3.8	7.39±.001	44.1±2	35.2±1.8	—

8.1% ± 1.5 is significant, $p<0.001$. As shown in Table 3, the arterial oxygen saturations in the nonsicklemic anemic patients ranged from 92.4 to 100% of capacity, only one falling below the range in the nonanemic subjects. The mean arterial saturation in the nonsicklemic anemic patients was 96% of capacity. This was significantly higher than in the sicklemic patients, $p<0.01$, and was not significantly different from the normal group, $p>0.4$.

During the breathing of ambient air, normal arterial oxygen tensions were 81 to 102 mm. Hg, mean 91 mm. ± 2.6, Table 1. Under the same conditions, arterial oxygen tensions of the sicklemia patients were 61 to 91 mm. Hg,

TABLE 3.—ARTERIAL BLOOD AND GAS DATA IN 8 ANEMIC PATIENTS BREATHING ROOM AIR

Patient, Age, Diagnosis	*Hb. gm./ 100 ml.*	*O_2 Saturation % Capacity*	*Arterial O_2 Tension mm.*	*Effective Alveolar pO_2 mm.*	*O_2 Alveolar-arterial Gradient mm.*	*Arterial pCO_2*
1. E.A., 46 Blood loss	3.8	92.4	80	101	21	38
2. M.B., 36 Blood loss	2.9	100	82	109	27	33
3. E.S., 22 Blood loss	8.1	98	101	104	3	37
4. W.L., 34 Blood loss	8.3	95	102	103	1	38
5. W.M.A., 36 Blood loss	3.7	96	85	94	9	42
6. A.K., 36 Nutritional	4.9	94.7	85	113	28	36
7. V.M., 34 Post-gastrectomy	7.9	95	94	94	0	41
8. E.E., 58 Multiple myeloma	6.0	97	84	109	25	34
Mean	5.7±0.77	96±0.82	89±3.1	103±2.5	14±4.3	37±1.1

TABLE 4.—EFFECT OF BREATHING 15.6% O_2 IN N_2 ON BLOOD OXYGENATION IN NORMAL SUBJECTS AND IN SICKLE CELL ANEMIA

	Arterial pCO_2, mm.		*Arterial pO_2, mm.*		*Arterial O_2 Sat. % Capacity*		*Alveolar-arterial pO_2 Gradient*	
	Normal	*Sicklemia*	*Normal*	*Sicklemia*	*Normal*	*Sicklemia*	*Sicklemia Ambient Air*	*Sicklemia 15.6% O_2*
	36	36	76	62	94	65	31.4	11.1
	43	42	58	56	90	78	8.1	1.8
	39	32	68	69	90	68	18.3	5.9
	41	29	68	76	92	81	21.8	2.8
	38	38	60	57	92	80	7.9	4.1
	44	29	60	64	86	78	25.3	8.6
Mean±S E	40.2±1.2	34.3±2.1	65±2.8	64±3.1	90.7±1.1	75±2.8	18.8±3.8	5:7±1.5
Mean Diff.±S E	5.9±2.5		1±4.2		15.7±3.0		13.1±4.1	
	$p = 0.05$		$p = 0.8$		$p = 0.001$		$p = 0.01$	

mean 78 mm. ± 2.9, Table 2. The mean difference in the normal and sicklemia groups of 13 ± 3.91 is significant, $p<0.01$. In the nonsicklemic anemic patients, Table 3, arterial pO_2 was 80 to 102 mm., mean 89 ± 3.1. This figure is not significantly different from the normal group, $p>0.5$, and is significantly higher than in the sicklemia group, $p<0.05$.

alveolar-arterial oxygen tension gradients in normal subjects were —4 to 14 mm. pO_2, mean 3.7 mm. ± 2.2, Table 1. In the sicklemia patients, Table 2, alveolar-arterial oxygen tension gradients were from 8 to 38 mm. pO_2, mean 22.9 ± 3.8. The mean difference between groups of 19.2 ± 4.35 is significant statistically, $p<0.001$. In the sickle cell anemia patients, a regression of alveolar-arterial oxygen tension gradient on hematocrit showed no significant association, $p>0.3$. In the nonsicklemic anemic patients, alveolar-arterial pO_2 gradients were a mean of 14, not significantly higher than the normal of 3.7 or significantly lower than the sicklemia value of 23, $p>0.1$ in each instance.

TABLE 5.—OXYGEN SATURATIONS OF NORMAL AND SICKLE HEMOGLOBIN
Matching pH ± 0.02 and O_2 Tension ± 3 mm.

	pH		*O_2 Tension mm.*		*O_2 Saturation % Capacity*		
	Normal	*Sickle*	*Normal*	*Sickle*	*Normal*	*Sickle*	*Diff.*
1.	7.43	7.42[1]	76	78	94	90	4
2.	7.31	7.31[2]	20	19	27	21	6
3.	7.39	7.39	88	91	95	91	4
4.	7.37	7.38	58	61	90	80	10
5.	7.20	7.22*	28	26	55	23	32
6.	7.40	7.40[1]	68	68	92	76	16
7.	7.41	7.39[1]	84	85	94	89	5
8.	7.39	7.38[3]	81	81	97	91	6
9.	7.40[3]	7.41	60	62	89	65	24
10.	7.34*	7.32*	22	20	40	24	16
11.	7.27*	7.26*[1]	64	64	87	79	8
12.	7.33*	7.31[2]	44	44	76	58	18
13.	7.29*	7.29[1]	68	66	91	73	18
14.	7.44*	7.43*	25	23	38	22	16
15.	7.36*	7.38*	84	84	92	88	4

* Tonometer equilibration values.
1. Average of two values.
2. Average of three values, one obtained by equilibration.
3. Average of three values.

During the breathing of ambient air, effective alveolar pO_2 in normal subjects was 85 to 99 mm. Hg, mean 95 mm. ± 1.8, Table 1. In the sicklemia patients, Table 2, effective alveolar pO_2 was 86 to 113 mm. Hg, mean 101 mm. ± 2.9. The mean difference of 6 ± 3.4 mm. is not significant statistically, $p<0.1$. Mean effective alveolar pO_2 in the nonsicklemic anemic patients was 103 mm., which was not significantly different from the sicklemic subjects, but was significantly higher than in the normal subjects, $p<0.05$.

During ambient air breathing, while breathing ambient air, normal subjects had an arterial pCO_2 of 38 to 45 mm., mean 42.4 mm. ± 1, Table 1. Sicklemia patients had an arterial pCO_2 of 28 to 43 mm. Hg, mean 35.2 ± 1.8, Table 2. The mean

difference of 7.2 ± 2.3 is significant statistically, $p<0.01$. The patients with nonsicklemic anemia had a pCO_2, Table 3, of 33 to 42 mm. The mean of 37 ± 1.1 was not significantly different from the mean in the sicklemic patients, but was significantly lower than the normal mean of 42.4, $p<0.02$.

While breathing ambient air, normal arterial blood pH was 7.30 to 7.41, mean 7.37 ± .013, Table 1. In sicklemia patients, arterial blood pH was 7.37 to 7.42, mean 7.39 ± .001, Table 2. The mean difference of .016 ± .014 is not significant statistically, $p>0.1$.

During the breathing of 15.6% oxygen, the following observations were made (Table 4). The arterial oxygen saturations in 6 normal subjects were 86 to 94% of capacity, mean 90.7%. In 6 sicklemia patients, the arterial oxygen saturations were 65 to 81% of capacity, mean 75%. The mean difference of 15.7 ± 3 is significant statistically, $p<0.001$. Arterial pO_2 in the normal subjects was from 58 to 76, mean 65. In the sicklemia subjects, arterial pO_2 was from 56 to 76, mean 64. The mean difference of 1 ± 4.2 is not significant, $p>0.8$. In 4 normal subjects, mean alveolar-arterial oxygen tension gradient was 3.4 breathing ambient air, and −0.6 mm. while breathing 15.6% oxygen. In the sickle cell anemia patients, the alveolar-arterial oxygen tension gradient during 15% oxygen breathing was 2 to 11, mean 5.7 ± 1.5. This is significantly less than the mean gradient of 18.8 while breathing ambient air in these same subjects, mean difference 13.1 ± 4.1, $p<0.01$.

Vital capacities were considerably reduced in each of 6 sicklemia patients tested (Table 2). Predicted vital capacities according to the regression formula of Baldwin, Cournand, and Richards[1] showed that these vital capacities were from 46 to 63% of the normal.

Chest roentgenograms were obtained in the sicklemia patients only. In patient G.B. there was slight cardiac enlargement and a density radiating from either hilum consistent with pulmonary edema. Patient W.W. had several fibrotic linear streaks throughout both lower lung fields. E.B. had moderate cardiac enlargement and a suggestion of fine reticular pulmonary fibrosis. The lung fields of patient F.B. appeared mildly congested. D.Y. had increased cardiac transverse diameter with prominence of the pulmonary artery. The other 4 chest films were considered normal, although the heart was at the upper limit of normal size in 3 of the 4.

In order to compare the saturation of oxyhemoglobin in normal and sicklemia patients, under conditions of comparable pH and oxygen tension, Table 5 was made. In each sample of normal blood where there was measurement of pH, O_2 tension and oxygen saturation, whether *in vivo* or by *in vitro* equilibration, an attempt was made to find one or more samples of sicklemia blood in which the pH varied from the normal sample by no more than ± 0.02 and the oxygen tension by no more than ±3 mm., since those values represent the limits of accuracy of the techniques employed. These values which matched were paired and are presented in Table 5. It may be seen that in each pair, the oxyhemoglobin saturaton of sickle hemoglobin is less than that of normal hemoglobin at comparable pH and oxygen tension: the normal hemoglobin had from 4% to 32% of capacity higher saturation with oxygen than did sickle hemoglobin at comparable pH and oxygen tension.

While breathing ambient air, ventilation per square meter per minute was 3529 to 4687 STP, mean 3880, in the normal subjects and was 3074 to 5853, mean 4256, in the sicklemia patients.

Discussion. The present study confirms that unsaturation of oxyhemoglobin is a frequent occurrence in sickle cell anemia; in none of our 9 subjects was the arterial oxygen saturation as high as in the lowest normal subject (93.7% of capacity). This is a higher incidence of abnormal arterial blood oxygen saturation than that reported by Leight, Snider, Clifford, and Hellems[11] who found arterial oxygen saturations below 94% in 9 of 13 patients with sickle cell anemia. Few studies have been reported of arterial oxygen saturation in other types of anemia. Himwich and Loebel observed normal resting arterial oxygen saturation solution in 4 subjects with anemia[9]. Rasmussen and Sturstein[14], however, found arterial oxygen saturation below 93% in 6 of 12 patients with anemia. Ryan and Hickam[18] did not describe the arterial oxyhemoglobin saturations in their study of the alveolar-arterial oxygen tension gradient in anemia. In our 8 subjects with nonsicklemic anemia, only one had arterial oxygen saturation below that found in our normal subjects.

This study shows that the average arterial oxygen tension is significantly lower than normal in sicklemia. Our observations also show that the effective alveolar pO_2 is not diminished in sicklemia, and that the low arterial pO_2 in sicklemia is due to an increased "alveolar-arterial gradient" of oxygen tension, similar to the findings of Ryan and Hickam[18] in other types of anemia. However, our group of nonsicklemic anemic patients although showing a higher alveolar-arterial pO_2 gradient than in the normal group, demonstrated a lower alveolar-arterial pO_2 gradient than did the sicklemia patients. Our sicklemia patients had a significantly lower arterial pO_2 than did the patients with other types of anemia. The significant lowering of the alveolar-arterial O_2 tension gradient by the breathing of 15.6% O_2 suggests that increased admixture of unsaturated blood may be responsible (Lilienthal *et al.*[12]). It should be noted that the arterial pO_2 in normal and in sicklemic subjects was not significantly different during the breathing of 15.6% O_2 in nitrogen, yet the arterial oxygen saturations were much higher in the normal group. Ryan and Hickam[18] also found a decrease in the alveolar-arterial oxygen tension gradient in their anemic subjects when breathing a low oxygen gas mixture. This venous admixture may be due to passage of pulmonary arterial blood through unaerated lung tissue, or to increased blood from bronchial and Thebesian veins entering the pulmonary veins and left atrium. In this connection, the lower than normal (89% of capacity) oxygen saturation of pulmonary venous blood in the patient with atrial septal defect and sicklemia is of interest. Unlike the observations of Ryan and Hickam in other types of anemia, we did not find a significant negative association between height of alveolar-arterial gradient and hematocrit in our sicklemia patients.

It is of interest that our sicklemia patients with elevated alveolar-arterial oxygen gradients had also other evidences of cardiopulmonary disease. Five had pulmonary Roentgen patterns suggestive of fibrosis or congestion, and in the majority, the heart was borderline in size or slightly enlarged. Roentgen evidence of cardiac enlargement was found in each of their 13 sicklemia patients by Leight and co-workers[11]. Where measured, our sicklemia patients had also considerable reduction in vital capacity. Whether this is related to pulmonary fibrosis, pulmonary hemosiderosis, pulmonary congestion, or anemia *per se*, is not clear. Blumgart, Gargill, and Gilligan[5]

have described reduction of vital capacity in anemia of other etiology.

The arterial carbon dioxide tension was significantly lower in the sicklemia patients and in the patients with other types of anemia than in the normal subjects. Low arterial pCO_2 due to hyperventilation in anemia has been described frequently. There are several possible explanations for this. Tissue hypoxia may play a small part. Barr and Peters[2] and Richards and Strauss[15] showed that the carbon dioxide dissociation curve is flattened in anemia, due to loss of the buffering action of hemoglobin. Thus a given volume of carbon dioxide entering the blood from the tissues tends to cause a greater than normal pH change. Hyperventilation defends against pH change by keeping arterial pCO_2 somewhat below normal. The loss of carbonic anhydrase in anemia may also cause hyperpnea because of tissue retention of carbon dioxide (Becklake *et al.*[3].)

The abnormality in oxygen uptake by hemoglobin of the sicklemia patients confirms the findings of Becklake, Griffiths, McGregor, Goldman, and Schreve[3] who found the oxyhemoglobin dissociation curve displaced to the right of the normal in 4 patients with sicklemia. This was not found in subjects with sickle cell trait. We did not include patients with sickle cell trait in our study. Becklake and co-workers[3] believed that the abnormal uptake of oxygen by sickle hemoglobin did not occur when the hemoglobin was studied in solution. They believed that something in the hemoglobin environment, possibly in the plasma, is responsible for the abnormal oxygen uptake by sickle hemoglobin. Kennedy and Valtes[10] found a slight displacement to the right of the oxyhemoglobin dissociation curve in megaloblastic and in hypochromic anemia.

Our study shows that the patient with sicklemia has two difficulties in properly oxygenating his blood. One is a pulmonary defect characterized by difficulty in maintaining a normal alveolar-arterial oxygen tension gradient. The second is a hemoglobin defect in which there is a deficient uptake of oxygen by sickle hemoglobin at a given oxygen tension, so that the dissociation curve of oxyhemoglobin is displaced to the right of normal.

Summary. Studies were made in 11 normal subjects, in 10 with sickle cell anemia, and in 8 with other types of anemia. All patients with sicklemia had a reduction in arterial oxygen saturation. As a group, these patients had low arterial oxygen tensions, and increased alveolar-arterial oxygen tension gradients. They also had low arterial carbon dioxide tensions. The increased alveolar-arterial oxygen tension gradients in these patients were reduced toward normal by breathing 15.6% oxygen. Studies of oxygen saturation of sickle and normal hemoglobin at comparable tensions and pH showed consistently a lower uptake of oxygen by sickle hemoglobin. The subjects with nonsicklemic anemia had a higher arterial pO_2 than the sicklemic patients, and all save one had a normal systemic arterial oxygen saturation. It is concluded that the low arterial oxygen saturation in sickle cell anemia is due to two factors; one, an increased alveolar-arterial oxygen tension gradient; the other, an abnormal oxyhemoglobin dissociation curve. Our patients with other types of anemia were able to maintain a relatively normal systemic arterial oxygen saturation because of a lower mean alveolar-arterial oxygen tension gradient than that seen in sicklemia, and because of the presence of a more nearly normal oxyhemoglobin dissociation curve.

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SUMMARIO IN INTERLINGUA

Oxygenation de Sanguine Arterial in Anemia a Cellulas Falciforme

Le studios hic reportate esseva facite in 11 subjectos normal, 10 patientes con anemia a cellulas falciforme, e 8 patientes con altere typos de anemia. Omne le 10 patientes con anemia a cellulas falciforme habeva reducite grados de saturation oxygenic del sanguine arterial. Iste patientes (prendite como un gruppo) habeva basse tension de oxygeno arterial e augmento del gradiente de tension oxygenic inter gas alveolar e sanguine arterial. Illes etiam habeva basse tension arterial de bioxydo de carbon. Le augmentate gradientes alveolo-arterial de tension oxygenic se reduceva verso valores normal sub le effecto del respiration de 15,6 pro cento de oxygeno. Studios del saturation oxygenic de hemoglobina a falciformia e de hemoglobina normal con comparabile valores de tension e de pH revelava uniformemente un reducite acceptation de oxygeno in hemoglobina a falciformia. Le subjectos con anemia non-falciforme habeva plus alte valores pro pO_2 arterial que le patientes con anemia a cellulas falciforme, e omnes, con un exception, habeva normal valores de saturation oxygenic in le sanguine arterial systemic. Es formulate le conclusion que le basse saturation oxygenic arterial in patientes con anemia a cellulas falciforme resulta de duo factores, *i.e.* (1) un augmento del gradiente alveolo-arterial del tension oxygenic e (2) un curva anormal del dissociation oxyhemoglobinic. Nostre patientes con altere typos de anemia se provava capace a mantener un relativemente normal saturation oxygenic in le arterias systemic a causa del plus basse valor medie pro le gradiente alveolo-arterial del tension oxygenic e a causa del presentia de un plus normal curva de dissociation oxyhemoglobinic.

A DOUBLE BLIND STUDY USING MANGANESE AGAINST PLACEBO IN RHEUMATOID ARTHRITIS*

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A PILOT study, using double blind technique with manganese against placebo, was done on 18 rheumatoid arthritis patients over a 2-month period. This study was done to determine whether manganese would have any observable effect on the course of rheumatoid arthritis and to evaluate the use of a new quantitative method for recording the activity of this disease.

Investigations on induced connective tissue syndromes by Comens[1,2] have recently shown that hydralazine in large dosage can produce a "rheumatic state" in man and animals. Hydralazine (a vasodilator drug employed in the treatment of arterial hypertension) appears to be unique in this respect. There is experimental evidence that the hydralazine syndrome in animals can be prevented and reversed by administration of small amounts of manganese, a trace element apparently related to certain enzyme systems essential for the integrity of connective tissue (Comens[2]). This important research by Comens, now in progress, led us to select manganese as a model therapeutic agent for the present pilot study.

Lansbury[3,4] has recently described a method for quantitating the systemic and articular manifestations of rheumatoid arthritis. Use of this method permits objective evaluation of the natural history of this disease and provides a tool for assessing the effect of varied therapies at different times and geographic locations. Special attention, then, was directed to compiling data for computing the articular and systemic indices during the course of this study.

Method of Study. Eighteen patients were selected from the arthritis clinic after careful evaluation by various members of the staff. These patients were chosen by using the Ropes' Committee criteria of "definite," "probable," or "possible" cases of rheumatoid arthritis; only "definite" cases were included in this study. The difficulty in obtaining suitable cases from a single clinic for drug testing became apparent in this clinical sampling. (This is one of the reasons for the necessity of a multi-clinic testing of any drug, with an objective and uniform method for evaluation of results.) All patients were on a basic program of rest, aspirin, exercises, and mild sedation, as necessary. Nine patients received capsule "A" three times a day, revealed by the hospital pharmacist after the completion of this study to contain 0.3 gm. manganese glycerophosphate. The other 9 persons received capsule "B," a lactose placebo. Four of the 9 who received "A" capsules and all of the "B" group were on

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gold therapy. These comparable series of patients were simultaneously evaluated by means of systemic and articular indices. The systemic index was based upon five criteria: 1) morning stiffness, 2) aspirin consumption, 3) fatigue, 4) grip strength, 5) Cutler sedimentation rate index. The articular index (joint spread) was computed by summation of joint grades of activity, as described by Lansbury[3].

Age distribution of the "A" group averaged 52.4 years, with a range of 31 to 60 years.

TABLE 1.—SUMMARY OF 18 RHEUMATOID ARTHRITIS PATIENTS

Response (Judged by Systemic Index)	*Number*	*Range (Of Systemic Index)*
	Manganese (A)	
"Improved"	5	−7 to −55
"Worse"	4	+2 to +9
	Placebo (B)	
"Improved	5	−1 to −42
"Worse"	4	+3 to +53

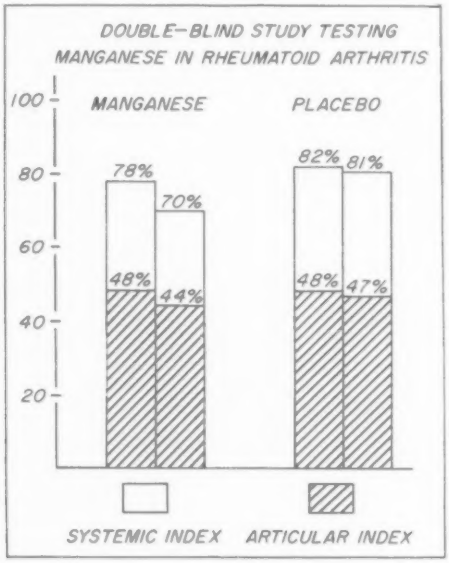

Fig. 1.

Of the "B" series, average age was 52.5, with a range of 40 to 70 years. The duration of rheumatoid arthritis for "A" group averaged 10.2 years (range 6 months to 30 years), and for "B," 6.1 years (range 1 to 17 years). The range of systemic indices for "A" at the beginning of our study was 50 to 118 (see bar graph, Fig. 1, an average of this range), and at conclusion of the study, 31 to 131. For the "B" group at onset of study, it was 53 to 157 (bar graph is the average); and at conclusion, 18 to 167.

Tabulation of individual case evaluations and total indices computed on four visits during the 2-month period of study are presented in Table 1.

Interpretation of Data. Dr. S. Michael Free, Statistician to Smith, Kline & French Laboratories of Philadelphia, collaborated in interpreting the data from this pilot study after its completion. The necessity of preliminary statistical advice in designing any clinical trial of a new therapeutic agent or method of evaluation, or both, was reemphasized in our study. The approximate sample sizes necessary for significance testing of systemic and articular indices were computed by Dr. Free from the control data (Table 2).

Sample size is dependent upon the effectiveness of the drug to be tested. In the case of manganese we did not take this into account and so selected too small a sample, as is evident from Table 2. Although there was a difference in the manganese group, this difference was less than the 15.5% required for the systemic index and 10.5% for the articular index to reach the level of statistical

significance. In this study of only 9 matched cases during a 2-month interval, no statistical significance could be attached to the observations because of the small sample size and expected variety of responses in any placebo group.

TABLE 2.—SAMPLE SIZES FOR SIGNIFICANCE OF AVERAGE DIFFERENCES IN DRUG TESTING* (S.M. Free)

	Average Difference Significantly Greater than Zero	
Sample Size	*Systemic Index*	*Articular Index*
10	15.5%	10.5%
20	10.9	7.4
30	8.9	6.1
40	7.7	5.2
50	6.9	4.7

*The above table is for testing one drug and showing the average change to be real. In comparing two drugs, one multiplies each tabulated percent difference by 1.4.

Summary. A pilot study using systemic and articular indices with a double blind technique was carried out on 18 carefully selected cases of rheumatoid arthritis over a 2-month period. Manganese was employed as a test agent against a placebo of similar appearance. It was found that manganese, though experimentally successful, was not clinically effective in this short term study of a chronic process. This study involved the use of an objective method for evaluating the course of rheumatoid arthritis and the design of a form for collecting pertinent data so that these could be statistically evaluated. Statistical analysis of collected data provided information for designing a larger scale study, particularly as to the number of cases required in testing for significance.

Although our series of nine paired patients was obviously too small to permit any definite conclusion, the present study demonstrates the application of this method. This disease, whose clinical manifestations which have heretofore been so difficult to assess, can now be categorized by an objective technique which we consider to be less cumbersome and more accurate than previous methods. The final test of this method for evaluating therapy in rheumatoid arthritis must be its ability to detect, in a double blind study, a statistically significant difference between a drug of known action and a placebo; this study used an unknown drug to evaluate an untested method.

A logical final step would be to apply the method in a multi-clinic test to evaluate corticosteroid substances, the effect of which is relatively well known, against placebos.

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(Interlingua on page 473)

EFFECTS OF L-ARGININE ON HEPATIC ENCEPHALOPATHY*

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The exact role of the elevated arterial blood ammonia in the production of hepatic encephalopathy is still indefinite. In patients with hepatic insufficiency of "exogenous origin," a fairly good correlation between arterial blood ammonia values and neurological changes has been reported (Eiseman, Bakewell and Clark[2], Gabuzda, Phillips and Davidson[6], McDermott and Adams[8], McDermott, Wareham and Riddell[9] and Phillips *et al.*[12]). In patients with hepatic encephalopathy of "endogenous origin," however, there is still considerable question as to whether the ammonia alone is responsible for the associated neurological disturbances, primarily because of the lack of correlation between the degree of cerebral dysfunction and blood ammonia levels (Eiseman, Bakewell and Clark[2], Fazekas *et al.*[4,5]). Since it is difficult to determine the degree of vascular shunting resulting from portal bed block or the exact amount of the exogenous accumulation of ammonia from dietary intake or gastrointestinal bleeding in any particular case, attempts have been made to treat all patients with hepatic encephalopathy by the administration of amino acids known to reduce the arterial blood ammonia level. As might be anticipated, varying results as to their therapeutic effectiveness have been reported (Eiseman, Bakewell and Clark[2], Fazekas, Ticktin and Shea[5], McDermott, Wareham and Riddell[9], Najarian and Harper[10], and Walshe[15,16]).

Previous studies have demonstrated a reduction of total cerebral oxygen consumption in patients with hepatic coma (Fazekas *et al.*[3,4,5]).

In this report, the effects of the administration of l-arginine on cerebral oxygen utilization, blood ammonia levels, blood urea nitrogen, as well as the clinical status of patients with hepatic encephalopathy are presented.

Method. Ten patients were studied, and in all cases there was laboratory and clinical evidence of severe hepatocellular insufficiency, the result of advanced cirrhosis. There were

*This investigation was supported by a research grant (PHS B–178) from the National Institute of Neurological Diseases and Blindness of the National Institutes of Health, Public Health Service.

varying degrees of cerebral dysfunction (lethargy or coma) at the time these studies were undertaken. Cerebral blood flow, oxygen consumption, and blood urea nitrogen were determined before and after the administration of from 25 to 37 gm. of l-arginine given over a period varying from one to 3 hours. Arterial blood ammonia determinations were also performed on these subjects before, and at various periods during and after the infusion of l-arginine. In 5 additional instances, only the influence of l-arginine on arterial blood ammonia levels was determined. The amino acid was dissolved in 10% dextrose and water in a concentration of 25 gm. per 500 ml.

Scheinberg and Stead's modification[13] of Kety and Schmidt's procedure[7] for the determination of cerebral blood flow was applied in this study. The oxygen content of the blood was determined by the manometric technique of Van Slyke and Neill[11]. Mean arterial pressure (MAP) was obtained directly from the femoral artery by means of a damped aneroid manometer (Alman and Fazekas[1]). Blood ammonia levels were determined by a microdiffusion nesslerization method modified from Seligson[14] on freshly drawn blood from the femoral artery and the jugular bulb. Blood was drawn without stasis into a previously calibrated 2 ml. syringe, and 1 ml. specimens were injected into each of two Seligson microdiffusion vessels within 15 to 45 seconds after withdrawal. In all cases a water blank was run with each pair of arterial and venous samples. Electroencephalograms were recorded on a six-channel Grass electroencephalograph in the conventional manner.

Results. Table 1 presents metabolic and clinical observations obtained before and after the infusion of l-arginine. The mean values demonstrate a reduction of cerebral oxygen utilization, mean arterial pressure, and an increase in arterial blood ammonia and blood urea nitrogen levels prior to the administration of the amino acid. The only significant metabolic changes noted during l-arginine infusion were a reduction in blood ammonia and an increase in blood urea nitrogen. The reduction in blood ammonia, although significant, was relatively small, and the lowest levels noted were in almost all instances still well above normal limits.

Table 2 presents serial ammonia determinations performed before, during, and at varying periods after the administration of the amino acid. The data demonstrate a significant fall of mean arterial blood ammonia values at ½, 1, and 2 hours after beginning the infusion. After 3 hours, there was no significant change from the pre-infusion level even though in 6 of the cases the infusion was continued for longer periods. In 9 instances, blood ammonia determinations were made 24 hours after termination of the infusion, and in only one case was the blood ammonia still significantly reduced from the pre-infusion level.

In 7 of the 10 subjects, there was no apparent change in the state of consciousness during the infusion of l-arginine which in 6 instances was continued for 4 hours or longer. Two subjects showed questionable improvement as evidenced by the development of spontaneity and coherence of speech while receiving l-arginine. One of these subjects (Case 1) succumbed within 72 hours even though he had received additional l-arginine for 2 days prior to his demise. The other subject (Case 4) became alert 48 hours after l-arginine administration and recovered sufficiently to be subsequently discharged. One comatose patient (Case 8) showed unquestionable improvement during l-arginine infusion. He became reactive, complained, and moved his extremities. Twenty-four hours later, he was again comatose and expired after 48 hours while again receiving l-arginine. Five of the 10 subjects improved sufficiently to permit their discharge, at least temporarily, from the hospital even though l-arginine administration had been discontinued for from 5 to 14 days. Ammonia values obtained in these 5

TABLE 1.—INFLUENCE OF L-ARGININE ON CEREBRAL AND AMMONIA METABOLISM

Case	Age (Yrs.)	CBF		$CMRO_2$		CVR		MAP		Art. NH_3		BUN		Dose I.V. (Gm.)	Period Given (Hrs.)	Clinical State	Clinical State After L-Arginine
		C	E	C	E	C	E	C	E	C	E	C	E				
1	53	28.6	32.2	1.7	1.5	2.5	3.4	71	111	2.4	1.9	39	45	25	2¾	Semicomatose	Able to talk coherently
		27.4	40.0	1.8	1.7	3.3	2.2	90	89	2.3	1.7	84	90	25	2	Semicomatose	Able to talk coherently
2	37	60.8	68.8	2.7	2.5	1.0	1.1	58	76	2.3	1.6	6	15	25	1	Lethargic	No change
3	37	90.4	86.8	1.6	1.4	0.8	0.9	76	76	2.4	2.0	10	26	25	2	Lethargic	No change
4	45	40.7	50.5	2.4	2.5	2.0	1.9	83	98	2.4	1.9	7	8	25	1½	Lethargic	Speech improved
5	54	59.8	60.9	1.6	1.4	2.1	2.3	124	139	4.0	2.0	34	37	25	1½	Semicomatose	No change
6	48	37.0	38.0	1.9	2.3	2.0	2.1	73	78	2.7	2.6			25	1½	Semicomatose	No change
7	56	40.1	34.1	1.4	1.4	1.5	1.6	59	56	1.8	1.5	21	28	27	2½	Semicomatose	No change
8	58	23.0	28.4	0.6	1.6	3.2	2.8	74	79	2.5	1.1	102	110	25	1¾	Comatose	Responsive
9	33	76.5	65.8	1.1	1.0	1.0	1.1	73	72	3.5	3.4	8	14	37	3	Lethargic	No change
10	53	35.2	43.7	1.6	1.4	2.7	2.3	96	100	3.3	2.0	48	62	25	2	Comatose	No change
										Mean Values							
	48	47.2	49.9	1.7	1.7	2.0	2.0	80	89	2.7	2.0*	36	44*	26			

* Significant difference, $p < .05$

CBF signifies cerebral blood flow in ml./100 gm. of brain/min.; $CMRO_2$, cerebral oxygen consumption in ml./100 gm. of brain/min.; CVR, cerebral vascular resistance in mm. of Hg/ml. blood/100 gm. of brain/min.; MAP, mean arterial blood pressure in mm. of Hg; Art. NH_3, arterial blood ammonia; BUN, blood urea nitrogen; C, before administration of l-arginine; and E, after administration of l-arginine.

TABLE 2.—EFFECT OF L-ARGININE ON BLOOD AMMONIA LEVELS IN PATIENTS WITH HEPATIC ENCEPHALOPATHY

Case	*Dates*	*Dose (Gm.)*	*Period Given (Hrs.)*	*Arterial NH_3*						*Remarks*
				Control	*½ hr.*	*1 hr.*	*2 hrs.*	*3 hrs.*	*2½ hrs.*	
1	12/26/56	25	2½	2.4	2.2	2.2	1.9		2.3	Speech improved
	12/27/56	25	2	2.3	2.0	1.9	1.7		2.1	Speech improved
	12/28/56	50	7	2.1		2.5	2.6	2.4		Expired 12/29/56
2	1/ 4/57	25	1	2.3	2.1	1.6		1.8	2.1	Alert; discharged 1/18/57
3	1/22/57	25	2	2.4	1.6	1.8	2.0	2.4	2.5	Alert; discharged 1/30/57
4	1/23/57	25	1½	2.4	2.8	1.9		2.0	2.6	Alert; discharged 2/12/57
5	2/25/57	25	1½	4.0	2.8	2.3	2.0	1.8	2.3	Alert; discharged 3/ 4/57
6	2/28/57	25	1½	2.7	2.7	2.0	2.6	3.4		Expired 3/3/57
7	1/10/57	50	5	1.8		1.4		1.5	2.1	Lethargic
	1/11/57	50	9	2.1		1.9		1.4	2.4	Lethargic
	3/ 4/57	50	6	1.8		1.8	1.5	1.1		Expired 3/5/57
8	3/18/57	25	1¾	2.5	1.5	1.5	1.1	1.8	4.7	Temporary improvement
	3/20/57	50	3	3.4	3.1	2.7	2.9	3.4		Expired 3/20/57
9	3/22/57	50	4	3.5	3.0	3.2	3.5	3.4		Signed out 3/27/57
10	4/ 6/57	39	6	3.3	2.7	1.5	2.0	2.7		Expired 4/6/57
				Mean Values						
		36		2.6	2.4*	2.0*	2.2*	2.2	2.6	

* Significant difference from control values, $p < .05$. The control means are as follows: ½-hour, 2.8; 1-hour, 2.6; and 2-hour, 2.8.

patients after remission of symptoms revealed no consistent or significant changes when compared to pre-treatment values. Repeat cerebral studies obtained in 2 of these 5 patients prior to discharge failed to demonstrate any significant change in cerebral oxygen utilization or change in abnormal slow wave electrical patterns previously noted.

Discussion. The reduction in arterial blood ammonia concentration following the administration of l-arginine, as well as temporary clinical improvement during l-arginine infusion, noted in 3 of our subjects, confirms in part the findings previously reported by Najarian and Harper[10]. It should be emphasized, however, that immediate clinical improvement did not occur in the majority of the cases in spite of a significant reduction in arterial blood ammonia but occurred subsequently in 5 subjects even though ammonia levels had risen to, or above, pre-infusion values. It may be that in these subjects supportive care, that is, the administration of blood, fluids, electrolytes, glucose and antibiotics, was largely responsible for the delayed remission. There can be no doubt, however, that elevation of blood ammonia may in some way interfere with cerebral energy production or utilization, since it would be difficult to otherwise explain periodic episodes of stupor or coma directly related to the ingestion of protein or ammonia salts (Gabuzda, Phillips and Davidson[6], McDermott and Adams[8], and Phillips *et al.*[12]) and the temporary improvement noted in certain cases after the administration of l-arginine.

As previously indicated, it is difficult to determine to what extent the encephalopathy may be due to the direct shunting of ammonia into the systemic circulation through veno-arterial or veno-veno channels, thus by-passing liver cells. It is possible that in some patients experiencing clinical remissions the shunting mechanisms may be primarily responsible for the elevated ammonia rather than a failure of the liver *per se*, since elevation of blood urea nitrogen following l-arginine administration indicates that the liver is still capable of urea synthesis. The high initial blood urea nitrogen noted in 3 of the subjects may be due to gastrointestinal bleeding, reduced renal blood flow, or associated renal disease. It is interesting that 2 of these showed temporary improvement after l-arginine administration. Histological examination of the kidney in Cases 8 and 10 failed to disclose renal pathology.

Previous studies have shown a consistent depression of total cerebral oxygen consumption in patients with hepatic encephalopathy (Fazekas *et al.*[3,4,5].) Since there is no decrease in oxygen delivery or reduction in the availability of glucose, the decreased cerebral oxygen utilization must be attributed to an interference in intermediate cerebral metabolism. The fact that clinical improvement was observed without concomitant elevation in cerebral oxygen utilization suggests that the basic metabolic defect was not completely corrected by simply reducing the blood ammonia level toward normal. If ammonia alone were responsible for the metabolic defect, one would expect a rise in the cerebral oxygen consumption with a fall in blood ammonia levels. Previous studies with l-glutamic acid have similarly failed to show any correlation between arterial blood ammonia levels and total cerebral oxygen consumption (Fazekas, Ticktin and Shea[5]). It is possible, however, that reduction of arterial blood ammonia may have caused a localized increase in cerebral oxygen utilization not reflected by total cerebral oxygen consumption measurements. Despite

the lack of correlation which exists between the state of consciousness, cerebral oxygen consumption, and ammonia concentration in the blood, it would nevertheless seem advisable to administer those amino acids which reduce blood ammonia to all patients with hepatic encephalopathy.

Summary and Conclusions. Total cerebral oxygen consumption and ammonia determinations were made on 10 subjects with hepatic encephalopathy before and after the intravenous administration of l-arginine. There was a significant but temporary reduction in arterial blood ammonia values after l-arginine but no change in cerebral oxygen consumption. Temporary clinical improvement was noted in 3 subjects during l-arginine infusion. Five of the 10 subjects experienced a delayed clinical remission which could not be directly attributed to the amino acid.

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SUMMARIO IN INTERLINGUA

Effectos de L-Arginina Super Encephalopathia Hepatic

Le total consumption cerebral de oxygeno e le contento de ammoniaco in sanguine arterial esseva determinate in 10 subjectos con encephalopathia hepatic ante e post le administration intravenose de l-arginina. Occurreva un significative sed transiente reduction del valores de ammoniaco in sanguine arterial post l-arginina sed nulle alteration in le consumption cerebral de oxygeno. Un melioration clinic de duration temporari esseva notate in 3 subjectos durante le infusion de l-arginina. Cinque del 10 subjectos experientiava un retardate remission clinic, sed isto non esseva attribuibile directemente al action del amino-acido.

PROGRESS
OF
MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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DEAFNESS SURGERY: AN EVALUATION

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PROGRESS in medicine over the past 20 years has been so dramatic that even many of our unfounded hopes have become accomplished facts. Otology has kept pace with this progress. Surgical correction of conductive deafness due to clinical otosclerosis has been successful in a majority of cases. Many of the techniques thus learned have been useful in correcting deafness due to other conductive causes. Much of this success has been due to the accomplishments of Lempert[14] who perfected a one-stage fenestration for otosclerosis. Credit is due also to Jenkins[10], Barany[1], Holmgren[6], Sourdille[30], and other otologists for their pioneer work in ideation.

Hallberg[4] has evaluated Lempert's contribution as follows: "Lempert's outstanding contribution was the devising of the tympanomeatal flap, a flap from the thin integument of the meatal wall, which could be placed over the fenestra made during the first operative procedure. This made it possible for the first time to take the procedure of fenestration from the domain of experimental surgery and place it in that of practical surgery."

However, fenestration became more routinely successful when the fenestra orginally created on the lateral semicircular canal was moved forward to the ampullar end of the canal on the surgical dome of the vestibule. This is the so-called fenestra nov-ovalis and the bone-dust free cupula technique for removal of the bony dome. An important by-product of this advance in deafness surgery has been the impetus given to meticulous temporal bone surgery for suppuration. Today, with antibiotics and magnification, aural surgeons are able to achieve conservation of hearing and even restoration

of hearing in the treatment of suppurative diseases rather than the destructive but life-saving surgical procedures. Another by-product has been the advances in the knowledge of cochlear and vestibular physiology[15].

The purpose of this evaluation is to present a historical review of some of the highlights of the advances of deafness surgery and to evaluate them in the light of my experiences. It has been my good fortune to be associated with fenestration surgery almost from its inception 20 years ago. When Lempert first reported his early fenestration cases in 1937 and 1938, the profession was highly skeptical as to the permanence of the results. One of the most serious handicaps to obtaining good results was the problem of osteogenetic repair and resultant closure of the fenestra. Among the first experimenters on animals in osteogenesis control were Lempert[16], Meltzer[21], Shambaugh[26] and Lindsay[20]. As stated above, the first real advance came when Lempert[17] moved the site of the fenestra forward from the lateral horizontal canal to the area over its ampullar end, the so-called surgical dome of the vestibule. This allowed for the creation of a wider fenestra over the vestibule of the labyrinth. The simple increase of wideness and depth led to an increase of long-term successes from about 30% to over 60% in ideal cases. The next phase of research by the pioneers was that of perfecting delicate performance of the fenestration to insure better results. Lempert was tireless in this direction and Shambaugh[27,28] merits our thanks for popularizing the use of the operating microscope, so long advised by Nylen[23] and Holmgren[7], and the introduction of constant irrigation during surgery. This effected a more meticulous fenestration with smooth eburnated edges and endochondralization and, finally, the achievement of a "bone dust free oval window." A combination of these techniques brought about a reduction of the number of cases with postoperative osteogenesis and postoperative labyrinthitis due to surgical manipulation of the membranous labyrinth. It also reduced the incidence of osteogenetic islands beginning in bone remnants left behind in the perilymph fluid.

The next problem was that of osteogenetic narrowing of the fenestra and filling of the opening with fibrous tissue with resultant dampening of hearing. Ring-like devices were contrived and cartilaginous stopples were used in an attempt to maintain the fenestra. These attempts generally failed to improve on the existing techniques until Lempert[18] devised the cupula technique. This consisted of burnishing the labyrinthine dome with dental polishing burrs until the oval outline of the fenestra appeared as a blue line. This blue line appearance is due to the thinness and translucence of the endosteal bone and endosteal membrane. The bone in the center of the oval is not thinned excessively and remains as a cupula. House[8] used only the double line, not completing the ring. At this point, sharp, spear-like knives are used to complete the fenestra and to open the window along the blue line in much the same manner as a sardine can opener is used. The cupula bone is then removed as a lid and the underlying fenestra is cleaned with no manipulation of the edges necessary. The technique obviated the need for concern over creation of bone dust. Thus, the problem of leaving a bone-dust free perilymph with little or no trauma to the labyrinth was solved. This resulted in a higher degree of success in controlling the problem of bone regeneration and reducing traumatic labyrinthine irritation.

Attention was next directed to the management of the osteal membrane and the placement of the flap. Lempert's earliest techniques called for attention to the need for a tense tightly packed flap over the fenestra. It is my belief that unconsciously he achieved adherence of the endosteal membrane to the flap at the bony edge of the window and limited the incidence of regeneration. Shambaugh called attention to the need of endosteal hemming to achieve this result. Lempert, in 1951, advised deliberate invagination of the flap into the fenestral opening. He achieved this by inserting a cotton plug the size and shape of the fenestra onto the flap and over the fenestra area and then invaginating the cotton plug with the flap into the opening of the fenestra, thus sealing the periosteal edge of the flap to the bony edge of the fenestra.

As a result of this research, fenestration surgery achieved the status of predictable, long-term maintenance of the new oval window to replace the ankylosed fenestral ovalis due to otosclerosis. At the present time the otologic surgeon can state with assurance that a meticulously performed fenestration with cupula and invagination technique will achieve a permanently opened fenestra. The only limitation in the results are the amount of secondary nerve degeneration associated with otosclerosis present in the individual patient and the amount of nerve degeneration created surgically by labyrinthine irritation. Therefore, in the past few years, research in fenestration surgery has been concerned primarily with the problem of reduced hearing due to secondary nerve degeneration from surgical trauma. This occurred in about 15% of the cases. Since the cupula technique allowed for a minimal amount of surgical manipulation of the membranous labyrinth, attention was directed to the irrigating solution as a source of irritation. Lamp[13] first attacked this problem with a balanced solution that matched the electrolyte and sugar composition of perilymph. Shambaugh[29] with Gey and Venker went a step further and are attempting to match perilymph not only electrolytically, but from the standpoint of protein content as well.

Lempert[19] has solved this problem by establishing what he calls a dry technique, abstaining from the use of any irrigating fluid. He makes this possible by first achieving complete hemostasis and secondly by performing a dry cupula removal of the surgical dome of the vestibule. With the absence of irrigating fluid the endolymphatic membrane is constantly bathed in its own perilymph and is thus in its natural state. He maintains that, when perfectly performed, this technique eliminates the need for irrigation. My recent cases using this technique bear out his contention. As a result of these advances it is possible to state that approximately 2 out of 3 patients who are ideally suited for fenestration surgery by reason of the fact that they have an air conduction loss of hearing due to clinical otosclerosis and normal bone conduction can be assured of a long-term restoration to the 25 decibel level or better. Furthermore restoration may be achieved to the 30 decibel level in about an additional 25% of the cases. Thus a total of about 9 out of 10 such patients may be assured of pracical hearing as a result of fenestration surgery.

Because of the technical difficulties of fenestration and the complication of postoperative vertigo in some patients, and the need for after care of the fenestration cavity, interest in the operation for mobilization of the ankylosed stapes has been revived.

This operation, first attempted in 1876 by Kessel[12], Jack[9] and others and revived in 1890 by Miot[22], has been reintroduced by Rosen[24] and his work has been enthusiastically received by many otologic surgeons. Rosen's operation consists of approaching the middle ear by elevating the drum in its posterior aspects out of the annulus as in the Lempert tympanosympathectomy and exposing the incudo-stapedial joint. He then manipulates the stapes so as to create a fracture through the otosclerotic process. Where the ankylosis is so severe as to prevent fracture by manipulation of the head and neck of the stapes, Rosen[24a] recently advised perforation of the footplate of the stapes so as to create a fenestration of the footplate. Goodhill[3a] has advised attacking the otosclerotic process directly at the footplate and creating a fracture line with picks. Mobilization of the stapes offers many advantages to patients. If successful, it entails overnight hospitalization with little or no after care. The incidence of complications are relatively few. Antibiotics, good magnification, and the increased knowledge of meticulous temporal bone surgery as a result of fenestration surgery have made possible the success in mobilization of the stapes. At any rate, the complications from this surgery have been minimal. Two factors, unfortunately, limit the results of this surgery: rehealing of the fracture of the otosclerotic process and the fact that the attack has been made at the site of the pathology and thus further ankylosis by the otosclerotic process can refix the stapes.

While it is difficult to speak of long-term results at this point, the present status of mobilization surgery makes it fair to state that 25% of the patients operated on with manipulation at the neck of the stapes can achieve restoration of practical hearing for a period longer than three months, which would ordinarily cover the time for reduction of hearing due to healing of the fracture. Better results may be achieved by either a direct attack on the otosclerotic process or by perforation of the footplate of the stapes[25]. At this time, however, it is the feeling of the author that most of these attacks will also seriously increase the incidence of complications from the surgery with further loss of hearing. It would seem that this is the result of labyrinthine irritation, injury or hemorrhage and that the percentage of patients made worse by perforation of the footplate must increase as well.

It seems fair to state that surgical correction of deafness due to otosclerosis is entirely an elective procedure. It cannot be classified with surgery for appendicitis or even carcinoma, for example. Therefore, it becomes important for the patient to have a full knowledge of the potentialities of surgical procedures so that he may choose whether to use a hearing aid or to have surgery for either stapes mobilization or fenestration. Each has its advantages and disadvantages that must be weighed according to the individual needs of the patient. In my experience, most mature patients who seek surgical correction of otosclerosis choose fenestration primarily for its long-term predictable results.

As was stated earlier, the meticulous techniques developed in deafness surgery have created a new interest in conservation and restoration of hearing in middle ear defects due to inflammatory diseases. In 1941, Woodruff[31] and I[5], at the suggestion of Lempert, first reported the use of the fenestration flap and the endaural mastoid and attic exposure as achieved in the fenestration operation for its use in attic cholesteatoma and in performing the modified attico-mastoidectomy as in the

Bondy procedure. With this operation, we were able to remove attic cholesteatoma and inflammatory diseases of the mastoid in order to preserve good hearing in appropriate cases. Later, Juers[11] pointed out that where the disease involved the ossicular change so as to necessitate removal of the incus and the head and neck of the malleus, hearing improvement could be obtained when the continuous tympanomeatal flap was placed in apposition to the head of the stapes, causing a myringostapediopexy.

Zollner[33], Wullstein[32], Freckner[2] and Gisselsson[3] in recent years have pointed out the necessity for performing microsurgery of middle ear disease, taking into consideration the physiologic principles learned through fenestration surgery for the mobility of the round and oval window. These principles make possible the correcting of tympanic perforations with tympanoplasty so as to have an intact drum membrane, the creation of a middle ear resonance chamber, and the maintenance of an ossicular chain sound conduction mechanism or its duplication with prosthesis if necessary. The correction of interference of movements of the round and oval window so that both windows are maintained as mobile units, allowing for phase difference so as to create movement of the basilar membrane, is also possible. In the event that the oval window is ankylosed as a result of chronic disease, a new oval window can be established by fenestration.

In summary, the fenestration operation for otosclerosis offers practical restoration of hearing for the conductively impeded patient with deafness due to otosclerosis or stapes fixation. In addition, the knowledge of this technique has made possible the advancement of microsurgery of the middle ear to include the achievement of successful mobilization of the stapes and the restoration and conservation of hearing in chronic suppurative disease with conductive deafness. Therefore, the knowledge of fenestration surgery technique is a keystone in the accomplishments of middle-ear surgery.

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SUMMARIO IN INTERLINGUA

(See page 459 for original article)

Un Studio Bis-Occulte con le Uso de Manganese e un Medication Fictitie in Arthritis Rheumatoide

Un studio-pilota, utilisante indices systemic e articular sub le conditiones de un technica bis-occulte, esseva effectuate con 18 cautemente seligite casos de arthritis rheumatoide durante un periodo de 2 menses. Manganese esseva usate como agente de experimentation juxta un medication fictitie de apparentia equal. Esseva constatate que managanese, ben que experimentalmente successose, non esseva clinicamente efficace in iste breve studio de un processo chronic. Le studio empleava un methodo objective pro le evalutation del curso de arthritis rheumatoide. Illo visava a elaborar un formulario pro le collection de datos pertinente con le objectivo de render los preste al interpretation statistic. Le analyse statistic del datos colligite contribueva informationes de valor in planar un plus extense studio, specialmente con respecto al numero de casos necessari pro assecurar le signification statistic del resultatos.

Ben que nostre serie 18 patientes (in 9 pares) esseva obviemente troppo parve pro permitter le formulation de conclusiones definite, le presente studio demonstra le application de iste methodo. Iste morbo, con manifestationes clinic que usque nunc esseva si difficile a evalutar, ha devenite categorisabile gratias a un technica objective que nos considera como minus ponderose e plus accurate que previe proponimentos. Le test supreme de iste methodo pro le evalutation de therapias contra arthritis rheumatoide debe esser su capacitate de deteger in un studio bis-occulte un statisticamente significative differentia inter un droga de cognoscite efficacia e un medication fictitie. Le presente studio usava un non-cognoscite droga pro evalutar un non-provate methodo.

Un passo final esserea logicamente le application del methodo in un test a plure clinicas pro le evalutation de substantias corticosteroide (le effecto del quales es relativemente ben cognoscite) in opposition a medicationes fictitie.

DERMATOLOGY AND SYPHILOLOGY

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SOME ASPECTS OF THE RELATIONSHIP OF CUTANEOUS AND GASTROINTESTINAL DISORDERS

A REVIEW OF RECENT LITERATURE

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AND

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THE frequent concomitance of cutaneous and gastrointestinal disorders has led clinicians to speculate about the reasons for such association. Although the gastrointestinal tract and skin do not share a similar embryologic origin (Arey[5], and others state that the epithelium and glands of the gastrointestinal tract arise from entoderm, whereas the epidermis and the appendages of the skin arise from ectoderm), connective tissue and the blood vessels arise from mesoderm, and the innervation of both arises from ectoderm. Therefore, it would appear that whatever connection there may be between skin and gastrointestinal tract is vascular and neural, primarily. Indeed, while many disorders of skin and bowel appear to be associated on this basis, a number of them appear to be related in a less obvious fashion. In still others, the relationship of the cutaneous and gastrointestinal manifestations is, as yet, completely unknown.

In addition to being joined at both ends to the skin, the gastrointestinal

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tract resembles skin in that both have an epithelial covering, associated glands, and vascular, neural, and supporting structures. Here the resemblance ends, for the skin functions primarily as a barrier, whereas the gut is a filter, acting in both an absorptive and excretory capacity.

Physiologically, the nervous system acts as a common denominator. The impact of emotion on the skin and gastrointestinal tract is known to anyone who has ever broken into a cold sweat and experienced a sudden urge to move the bowels when faced with a stressful situation.

Pathologically, disorders of skin and gastrointestinal tract frequently may occur together as mere coincidence, both systems may be affected by the same disease, or disease in one system may predispose to disease in the other. The possible combinations of cutaneous and gastrointestinal disease may be categorized as follows:

1. Those primarily involving the skin, and involving the gastrointestinal tract secondarily.

2. Those primarily involving the gastrointestinal tract, and affecting the skin secondarily.

3. Those primarily in the viscera, but with coincidental involvement of the skin or the gastrointestinal tract, or both, although not always simultaneously.

4. Those cutaneous and gastrointestinal disorders which occur together but whose relationship is undetermined.

In this review we intend to point out briefly the cutaneous and gastrointestinal correlates as exemplified by the recent literature. The number of processes exhibiting these relationships is so great that only a selected group will be given special attention. Among the omissions, for example, are discussions on allergy, acne vulgaris, sarcoidosis (liver and skin), and von Recklinghausen's disease. Psychogenous processes, except for pruritus ani, will be only mentioned in passing. Metastatic malignancy from the gastrointestinal tract to the skin were described recently (Beerman, H., Am. J. Med. Sci., 233, 456, 1957). It is obvious from even a small experience that ulcerative colitis may be associated with a variety of dermatoses (aphthae, urticaria, petechiae, pigmentary disturbances, angiitis, and pyoderma gangrenosum, for example). Only pyoderma gangrenosum and angiitis will be delineated because these come nearest to being a "specific" cutaneous counterpart of ulcerative colitis.

It is apparent that the cutaneous expression of gastrointestinal disease may be an important suspicion arouser. This can well be seen in the case of Grey-Turner's sign, in which there is seen a localized blue, green, or yellow discoloration in the loin or about the umbilicus due to intraperitoneal hemorrhage associated with acute hemorrhagic pancreatitis. Likewise, acanthosis nigricans may point to a gastrointestinal malignancy.

DISEASES PRIMARY IN THE SKIN, WITH SECONDARY INVOLVEMENT OF THE GASTROINTESTINAL TRACT. It should be emphasized that instances of primary cutaneous disorders causing, or being associated with, gastrointestinal disease are extremely rare. Urbach[48] mentions only one such case, quoting Puntoni's report of epithelial sloughing of the bowel of an animal whose skin was coated experimentally with varnish.

Curling's ulcer may be considered a consequence of a cutaneous disorder. It is an ulcer of the duodenum which may follow extensive burns of the skin, and is believed to be due to the attendant hyperacidity and hyperemia of

the gastrointestinal tract produced by the shock.

Liver disease can occur as a result of absorption through the skin of hepato-toxic substances such as thallium, gold, arsenic, and antimony[52]. The severe gastrointestinal effects often seen in the past with arsenicals and mercurials in the treatment of syphilis are well known.

Exfoliative dermatitis may be a complication of a cutaneous disorder, or a cutaneous manifestation of an internal disease such as lymphoma or an intoxication. Weiner states that in either case the syndrome is so uniform that even the histologic characteristics may become indistinguishable[51]. It is surprising that generalized exfoliative dermatitis causes little systemic derangement, even in chronic cases. Such is the case, however, and although scattered reports mention such symptoms as anorexia, nausea, and diarrhea, there is no clear pattern associated with primary exfoliative dermatitis.

DISORDERS PRIMARILY IN THE GASTROINTESTINAL TRACT AND SECONDARY IN THE SKIN. There are a number of dermatoses that are caused by gastrointestinal diseases, or are associated in a known way. Some of these are characteristic, but others are nonspecific and variable.

Avitaminoses. Vitamin deficiencies are difficult to study because man does not ordinarily suffer from a lack of a single vitamin, and because the essential effects of vitamins are exceedingly subtle. Nevertheless, there are some cutaneous manifestations which can be clearly attributed to specific vitamin deficiencies caused by failure of absorption by the gastrointestinal tract, or by dietary deficiency. Vitamin A deficiency undoubtedly causes exaggerated keratinization of epithelial structures such as the eye, the skin, and the respiratory tract. Phrynoderma is a dermatosis consisting of dry skin, and perifollicular papules with a central keratotic plug. According to Weiner[51], and others, this condition responds to massive doses of vitamin A. However, Pillsbury, Shelley, and Kligman[34] point out that in this country lack of vitamin A is rare, and they feel that most cases of hyperkeratoses do not respond to vitamin A. They further point out that in certain rather rare dermatoses, such as Darier's disease, and pityriasis rubra pilaris, the present dosages employed are so large as to act pharmacologically, rather than physiologically.

Riboflavin deficiency is believed by many to be the cause of perleche, and while prolonged deficiency can cause cheilosis, glossitis, and fissures at the angles of the mouth, dental abnormalities, malocclusion, and contact dermatitis are far more commonly the real cause[31,34,51]. Nicotinic acid deficiency is thought to cause pellagra, which is characterized by glossitis, stomatitis, and a peculiar dermatitis which appears most commonly on exposed surfaces, seemingly in response to almost any form of local trauma, including light, heat, pressure, and friction. The lesions vary in severity, but may be vesico-bullous, and heal with atrophy and hyperpigmentation[34,51].

Sprue, which is an absorptive disorder of the bowel responding to parenteral vitamin B_{12} or folic acid, may be accompanied by stomatitis, glossitis, dry, pale skin, and chloasma-like hyperpigmentation, according to Weiner[52].

Functioning Carcinoid of the Bowel. Certain small tumors of the bowel, called argentaffinomas or carcinoids, have been known for many years by the surgeon and the pathologist. Carcinoids were classified as benign or malignant by the usual standards, but

were not believed to be functioning tumors. However, in 1953, Leinbeck isolated a substance from a carcinoid tumor which was pharmacologically active. Review of the literature revealed many cases of carcinoid associated with cutaneous vasomotor, cardiovascular, and gastrointestinal disturbances, all of which could be attributed to the pharmacologic action of the active substance isolated from these tumors, called serotonin. Serotonin is derived from tryptophane, and is a stimulator of smooth muscle. Normally only about 1% of tryptophane is converted to serotonin, but when a functioning carcinoid is present, up to 60% may be converted. There is a simple color test to detect serotonin in the urine. The outstanding features of functioning carcinoid are diarrhea, flushing and burning of the skin, cyanosis, increased blood pressure and cardiac sounds, hyperpnea, and tachypnea. Functioning carcinoids occur in about 25% of malignant carcinoids, and are chiefly found in the ileum[31,43].

Liver Diseases. Liver disease may be reflected in the skin in various ways. Jaundice, whether due to mechanical obstruction of bile flow, or to parenchymatous liver damage, is frequently the first clinical sign of serious internal disorders, particularly abdominal neoplasms. However, the skin may reflect liver damage in other ways, because of the complex relationship of liver function to general body metabolism. Ayres, Ayres, and Mirovitch[6] discuss an eczematous dermatitis seen in association with liver disorders which responded favorably to therapy directed at the hepatic dysfunction.

Xanthomatous eruptions have been observed frequently in biliary cirrhosis, and Shay and Harris[42] feel that such xanthomata, whether the cirrhosis is due to hepatocellular damage or extrabiliary obstruction, are secondary to the induced hypercholesterolemia.

Hicks and Mullins[26] discuss pruritus in liver disease, and believe that the often intractable itching seen in biliary cirrhosis months and years before the onset of jaundice or xanthomata is due to retention of estrogens normally excreted by the liver, perhaps in conjunction with elevated serum cholesterol. Other signs of liver disease include spider nevi and erythema palmare. Both are attributed to elevated estrogens.

Hepatic porphyria is a congenital metabolic disorder of the liver. It manifests itself in two ways. Acute porphyria is characterized by severe neurologic involvement, porphyrinuria, and is usually fatal, but there is no true photosensitivity, and skin changes are insignificant. Chronic porphyria, or porphyria cutanea tarda, is characterized by a true light sensitivity, and a dermatosis which may vary from a banal eczematous dermatitis to a severe bullous eruption. Porphyrinuria also occurs.

Ulcerative Colitis and Pyoderma Gangrenosum. Pyoderma gangrenosum is classically associated with ulcerative colitis, although this skin condition occurs in other debilitating states. The disease waxes and wanes with the course of the ulcerative colitis, and has been cured by extirpation of the diseased bowel[38]. The skin lesion, while not pathognomonic, is sufficiently distinctive to suggest the diagnosis. Pyoderma gangrenosum begins as a furuncle or a pustule which enlarges, breaks down, and ulcerates. The violaceous, undermined border, the virulence and resistance to therapy, and the fluctuation of the skin lesion with the patient's general state are strongly suggestive characteristics[22]. In 1941, Greenbaum[23] reviewed the literature, taking exception to the

term "gangrene" because of the molecular nature of the destruction, and attempting to assay the relationship of bacteria and their products to this disease. He felt that while bacteria played a major role in the pathogenesis of pyoderma gangrenosum, other factors, perhaps allergic, were contributory. More recently, others have suggested an allergic mechanism[18], perhaps an allergic vasculitis[22,50]. Rostenberg[39] considers that the Shwartzman reaction is the most logical pathogenetic explanation for pyoderma gangrenosum and ulcerative colitis, among other conditions, that has so far been advanced. On the other hand, pyoderma gangrenosum is not the only skin lesion seen with ulcerative colitis. Samitz and Greenberg[40] found an incidence of 34% of 189 cases of ulcerative colitis had one or more skin lesions. These included aphthous stomatitis, 30%; ulcerations and pyodermas, 24%; urticaria, 17%; and erythema nodosum, 12%. Therapy is a major problem in pyoderma gangrenosum. Antibiotics and chemotherapy are of little value in this condition, as Brunsting[16] and Ricketts[38] point out. Pyoderma gangrenosum best responds to treatment of the underlying disease. (Perry and Brunsting [Perry, H. O., and Brunsting, L. A.: A.M.A. Arch. Dermat., **75,** 380, 1957] reviewed the clinical and laboratory features of 19 cases of pyoderma gangrenosum. Since in only 11 [approximately 60%] was there clinical and laboratory evidence of chronic ulcerative colitis, it would appear that pyoderma gangrenosum is not invariably associated with disease of the bowel.)

Pruritus Ani. Pruritus ani, as well as pruritus of the perineum, vulva, and scrotum, may be secondary to such conditions as parasitic infestations, hemorrhoids, allergic states, or uncleanliness, but is most commonly psychogenous in origin. The latter problem is not within the scope of this paper. It is discussed at length by such authors as MacAlpine[29] and Obermayer[32]. These investigators do mention that psychogenous pruritus ani is frequently associated with bizarre gastrointestinal complaints. Pruritus ani may be a symptom of intestinal parasitic infestations such as oxyuriasis, and tapeworm infections, or may be associated with ano-rectal diseases such as hemorrhoids, fissure-in-ano, and other similar local conditions. One is always obliged to study patients with this complaint thoroughly. It is the frustrating experience of most clinicians, however, to find no demonstrable cause for the pruritus and to resort to purely symptomatic therapy. This includes the administration of corticoids, Roentgen rays, and various topical anesthetics.

Cutaneous Amebiasis. Amebiasis of the gastrointestinal tract may rarely have cutaneous manifestations[54]. Cutaneous amebiasis may be divided into three types.

1. Those cases following surgery, or associated with rupture of an abscess, with subsequent involvement of the skin.

2. Cases involving perianal skin, and associated with amebic colitis.

3. Cases having no direct contiguity with visceral amebiasis, and thus suggesting primary cutaneous amebiasis. Clinically, the lesions are progressive, ulcerative processes, with dark-red, indurated borders, and necrotic bases. The causative organisms may be found in the margins of the lesions by biopsy. Pierini and Borda[33] felt that there were definitely allergic manifestations of amebiasis, and that *Endolimax nana* and *Entamoeba coli* were also pathogenic, but these findings have not been confirmed. Emetine is the drug of choice in amebiasis, but the broad

spectrum antibiotics, in conjunction with chloroquin may be as effective[34].

Intoxications. Urbach[48] states that the nature of the cutaneous reaction seen with gastrointestinal disturbances seems to be a function of the predisposition of the skin of the individual rather than the nature of the excitant. Thus a particular excitant may produce eczema, erythema, urticaria, pruritus, or angioneurotic edema. But what are excitants, and how do they excite? Are foods toxic, or allergenic? Do dysfunction and anatomic disease of the gastrointestinal tract cause cutaneous disorders, and are toxic products of pathogenic bacterial flora or of intestinal putrefaction absorbed? All of these factors seem to play a role, as Urbach points out[48]. Stokes and Pillsbury[44] proposed a mechanism whereby the nervous system was the underlying cause of gastrointestinal disturbances, which in turn gave rise to various cutaneous manifestations. Many investigators who have attributed such disorders as rosacea, acne vulgaris, and seborrhea to gastrointestinal dysfunction, have tried dietotherapy, colonic irrigations, sterilization of the bowel, or alteration of the intestinal flora[2,48]. Urbach[48] reviewed the significance and the effects of these modalities, and concluded that the fundamental effect is achieved by the change itself, rather than the type of change.

VISCERAL DISEASE, WITH COINCIDENTAL INVOLVEMENT OF SKIN AND GASTROINTESTINAL TRACT. There are many systemic diseases which may involve either the skin, the gastrointestinal tract, or both impartially. Many of them are characterized by specific and readily recognizable cutaneous changes, which are of diagnostic importance to the internist.

Amyloidosis. Amyloidosis is a rare condition characterized by the deposition in the skin and other organs of an amorphous, incompletely identified, protein-like substance called amyloid, and which has certain staining characteristics. Amyloidosis may be primary in the skin, or may be a systemic disease, occurring as a sequela to chronic osteomyelitis, tuberculosis, syphilis, or multiple myeloma. Systemic amyloidosis can also occur in the absence of any demonstrable systemic disease, and this form is called primary systemic amyloidosis. The commonest lesions in the latter condition are macroglossia, and glossitis[34].

Lichen amyloidosis, or primary cutaneous amyloidosis, is characterized by markedly pruritic, translucent papules[24]. Although the lesions are clinically characteristic, histologic confirmation is necessary. Amyloid, wherever found, has certain peculiar staining properties which identify it[53]. Methyl violet stains amyloid a metachromatic bright red, iodine stains it brown, and with the van Gieson stain, it is yellow. Congo red is taken up *in vivo* by amyloid, hence the rate of disappearance from the serum of Congo red dye is used as a test for systemic amyloidosis. The dye may be taken up by cutaneous lesions, but the test is unreliable in primary cutaneous amyloidosis.

Bacterial and Mycotic Infections. Bacterial and mycotic infections may be primary in the skin, with or without systemic involvement, or they may arise secondarily from an internal focus. A third possibility is the so-called "id" eruption, sterile in itself, but indicative of a primary infection somewhere in the body, and considered to be an allergic manifestation. This entire subject has been summarized by Pillsbury, Shelley, and Kligman elsewhere[34], but we will consider several typical examples of systemic infections which affect the skin and gastrointestinal tract.

Typhoid fever is a classic example of a systemic infection involving the gastrointestinal tract and skin. Rose spots on the skin, with fever, malaise, gastrointestinal disturbances, and positive blood, stool, and urine cultures are much less common now, but are well remembered.

Tuberculosis is the prototype of the infections which may cause primary, secondary, or allergic skin manifestations. Primary inoculation tuberculosis does not concern us in this discussion because it acts like a primary pulmonary complex, usually evoking sufficient immunity to localize the lesion. However, there are a number of forms of secondary cutaneous tuberculosis which arise either from internal foci, or which represent cutaneous inoculation in persons who have previously had tuberculosis. Lupus vulgaris is suggested by a chronic, scarring, indolent lesion, usually on the face, which shows a marked tendency to extend peripherally but remains active within the scar. Tuberculids represent hypersensitivity reactions, according to Pillsbury, Shelley, and Kligman[34], and must meet certain criteria. They must have a tuberculoid histologic structure, the patient must have a positive tuberculin test, the lesions must fit one of the clinical, validated forms of tuberculid, and there must be a demonstrable primary focus. Papulonecrotic tuberculid is an example of this form of tuberculosis. It consists of clusters of papules which become pustular and then necrotic. Needless to say, treatment of both secondary cutaneous tuberculosis and of tuberculids is directed toward the primary infection.

The deep, or systemic mycoses generally act somewhat like tuberculosis, but most commonly involve organs other than the gastrointestinal tract. A notable exception is actinomycosis which has three forms, of which two involve the gastrointestinal tract initially. Cervico-facial actinomycosis begins in the mouth, usually around a carious tooth, and spreads through the soft tissues, eventually forming sinus tracts draining onto the face or neck. Abdominal actinomycosis begins in the bowel, spreads through the wall of the intestine, and may eventually involve other viscera, or form sinus tracts draining onto the skin. This form frequently begins at the ileocecal region, and may simulate appendicitis[34]. Vigorous antibiotic therapy with surgical excision comprise the treatment for actinomycosis.

Hereditary Hemorrhagic Telangiectasia. Also known as the Rendu-Weber-Osler syndrome, hereditary hemorrhagic telangiectasia affects the capillaries of the skin, and mucous membranes[8]. The cutaneous lesions resemble spider nevi, but do not pulsate, and do not fade on pressure. Because these lesions appear in the gastrointestinal tract, and severe hemorrhage may result, one should bear this condition in mind. The Rendu-Weber-Osler syndrome is inherited as a fully penetrant, single, nonsex-linked character[34].

Kaposi's Multiple Idiopathic Hemorrhagic Sarcoma. Kaposi's sarcoma appears to be a relatively benign proliferation of perithelial cells, with multicentric origins, and a tendency to occasional late sarcomatous change. Because the lesions arise from the cells surrounding the blood vessels, the tumors may be found anywhere. While the lesions are most commonly found in the skin, especially on the lower extremities, tumors may arise in the gastrointestinal tract, as well as elsewhere. These lesions may cause symptoms and signs on a purely mechanical basis, when systemic, or rarely, sarcomatous degeneration may occur[34].

Periarteritis Nodosa. Periarteritis

nodosa is a multiple system disease, characterized by fever, arthralgia, hypertension, weight loss, and a variety of other signs and symptoms due to involvement of the gastrointestinal tract, respiratory tract, nervous system, and the skin[50]. It is a disease of the smaller arteries, arterioles, and venules, causing occlusion of these vessels, and resulting in damage and death of the tissues subserved[4]. While skin lesions generally have a characteristic appearance and are readily recognizable, systemic involvement is often most difficult to diagnose clinically. The skin presents lesions which may be erythematous, nodular, urticarial, or even ulcerative. Gastrointestinal signs and symptoms depend upon the vascular changes, and generally consist of infarcts, resulting in necrosis of the portion of bowel, with ulceration and hemorrhage. The cause of the angiitis is unknown, but present theory strongly favors an allergic mechanism, with the vessels as the shock organ.

Pseudoxanthoma Elasticum. Szymanski and Caro[46] recently reviewed the relationship of this disease to internal diseases. They point out that pseudoxanthoma elasticum, once believed to be little more than a cosmetic defect, is in reality a cutaneous manifestation of a widespread disorder of elastic tissue. A rare disease, pseudoxanthoma elasticum is characterized by diagnostic skin lesions, angioid streaks in the retina, and occasional systemic vascular disorder such as gastrointestinal hemorrhage, which is usually severe and may resemble the hemorrhage of peptic ulcer.

Dermatomyositis. Dermatomyositis is a relatively rare disease of unknown cause. It is characterized by degeneration of connective tissue accompanied by wasting of skeletal muscle, and perhaps of cardiac muscle as well. Scattered, unconfirmed reports of gastrointestinal lesions such as ulcers of the colon, esophagus, and duodenum, erosions, ecchymoses, and necrosis of the gastric mucosa have appeared in the literature (compiled by Wainger and Lever[49], and Dowling[21]). Wainger and Lever attributed the gastrointestinal changes to vascular disease consisting of intimal thickening and thrombosis of small arteries and arterioles. Ordinarily, however, there does not appear to be a constant association of cutaneous and bowel involvement in this disease.

In the past, dermatomyositis frequently has been said to be associated with internal malignancy. Recently, however, Christianson, Brunsting, and Perry[17] have challenged this concept. In a series of 270 cases, they found an incidence of associated malignancies of 6.7%, all of which occurred in their respective age groups as found in the general population. It was the authors' feeling that the association of dermatomyositis and malignancy was incidental. Gastrointestinal signs and symptoms reported by Christianson *et al.* included hemorrhage, perforation, dysphagia, pain, and abdominal adhesions. They also observed a pityriasis rubra pilaris-like eruption in one case, and emphasize that the cutaneous manifestations of dermatomyositis are varied and nonspecific.

Lupus Erythematosus. Systemic lupus erythematosus is another disease of unknown cause. It affects the connective tissue throughout the body, and is usually classified with dermatomyositis and scleroderma. Gastrointestinal signs and symptoms are rare but significant. Occasionally, acute intestinal and peritoneal edema and inflammation may cause a syndrome strongly suggestive of a surgical emergency of the abdomen. Diarrhea may occur. Oral lesions, consisting of circumscribed red patches on the

mucosa, covered by a thin yellow exudate, occurs in about 25% of the cases[51]. Since the oral lesions reportedly occur twice as frequently in the more serious cases, their presence is considered a poor prognostic omen. However, oral lesions can occur in the chronic discoid form, which ordinarily has a much better prognosis.

Brown, Shirey and Haserick (**Brown, C. H., Shirey, E. K.,** and **Haserick, J. R.:** Gastroenterology, **31**, 649, 1956) found that 32 of 87 patients with systemic lupus erythematosus had such gastrointestinal symptoms as nausea and vomiting, flatulence, epigastric distress, diarrhea, abdominal tenderness, cramps, hematemesis, and pain in the right flank. In 25 these symptoms were mild, infrequent and not a therapeutic problem. The remaining 7 patients, all women, had severe gastrointestinal symptoms that were among their predominant complaints and constituted major problems in diagnosis and treatment. All 7 received steroid therapy after the diagnosis of lupus erythematosus was made. Five of them were considered to have an adynamic or paralytic ileus, which was confirmed by roentgenography in all and additionally by operation in one. Three of the 5 had dilatation of the second and third parts of the duodenum; one had a dilated, atonic stomach; and one had segmental dilatation of the jejunum. The ileus was temporary, and no obstructive lesion was found. Three of the 5 patients responded favorably to frequent feedings and administration of antacids. A perforated ulcer occurred in the fourth patient, who was not given ulcer treatment. The fifth patient, who had a dilated jejunum, was subjected to jejunotomy with evacuation of food and food residue from the dilated jejunum and immediate closure of the wound. Brown and his colleagues felt that collagen deposition in the submucosa, vascular changes associated with lupus erythematosus as the primary disease, or localized neurogenic phenomenon offer the most likely explanation of the causation of the segmental temporary ileus in these patients.

The remaining 2 patients had ulcerative colitis associated with their lupus erythematosus. One of these in addition had severe liver disease manifested by jaundice, spider nevi, positive flocculation tests, and an increased prothrombin time that did not respond to vitamin K therapy. Eleven of the 87 patients with lupus erythematosus were subjected to necropsy. The gastrointestinal findings were normal in 9. Interstitial edema and submucosal hemorrhage of the small intestine were found in one, and there was collagen deposition in the submucosa of the stomach in one.

Scleroderma. Scleroderma of the diffuse type belongs to the group of diseases presently called "collagen diseases." Basically a visceral disease, scleroderma affects the skin and the gastrointestinal tract in the same way. There occurs a thickening and condensation of the collagen, with secondary atrophy of the appendages, such as glands, and of the vessels. The cutaneous manifestations of diffuse scleroderma are well known, and include thickening of the skin generally, a glossy waxy appearance, and a feeling by the patient of a sensation of tightness, particularly of the hands and face. The bowel may be affected anywhere along its entire length, but favorite sites include the esophagus and the third portion of the duodenum. Beerman[10], in 1948, reviewed the literature concerning scleroderma, and emphasized the visceral changes, particularly with regard to the gastro-

intestinal tract. Dilation of the lower portion of the esophagus, dysphagia, and marked delay in passage of a barium meal were the chief lesions found. In the bowel, roentgenologic signs were quite distinctive. Localized widening of loops of bowel, decreased peristalsis, and delay in the passage of the barium meal were marked. Pugh also described the roentgenologic findings in diffuse scleroderma, mentioning also a noticeable rigidity of the bowel[36]. Beigelman, Goldner, and Bayles[13] reviewed 15 cases of diffuse scleroderma in 1953, and emphasized the histologic picture of the disease. They feel that the term "scleroderma" is a misnomer and minimizes the systemic character of the disorder. They supported Goetz in a proposal to substitute the term "progressive systemic sclerosis."

More recently, Abrams, Carnes, and Eaton[1] discussed the alimentary lesions of scleroderma. They pointed out that although gastrointestinal involvement occurs later than cutaneous disease, the onset of gastrointestinal signs and symptoms often presages a rapidly fatal course. Piper and Helwig[35] reviewed 31 necropsy cases of scleroderma, analyzing particularly the degree of visceral involvement. They emphasize the lack of specificity of clinical signs and symptoms of visceral scleroderma. The treatment of diffuse scleroderma is symptomatic, and of little avail.

ASSOCIATED CUTANEOUS AND GASTROINTESTINAL DISEASE BUT RELATIONSHIP OF THE MANIFESTATIONS UNDETERMINED. *Acanthosis Nigricans.* Acanthosis nigricans is an almost unique condition, being benign in itself, but having grave implications under certain circumstances. There are two types of acanthosis nigricans, histologically identical, differing in only one respect: association with internal malignancy. According to Curth[19], one form commonly arises after puberty, progresses unremittingly, and is invariably associated with an adenocarcinoma, 95% of which occur in the gastrointestinal tract, the remainder in the breast and lung. This form of acanthosis nigricans is called "malignant acanthosis nigricans" because of the association with internal malignancy, which seems to be even more malignant than its counterpart in the individual without acanthosis nigricans. It is interesting that malignant acanthosis nigricans improves when the internal malignancy is treated.

The second form, called "benign acanthosis nigricans," usually arises before puberty, tends to regress after adolescence, and is never seen with adenocarcinoma. It should be understood that the lack of development of an adenocarcinoma defines the benign form; there is no other difference. Malignant acanthosis nigricans may appear before, after, or during the appearance of the adenocarcinoma, and if present at the same time, will regress when the malignancy is extirpated. It is believed that the cancer is not the cause of the skin lesion, but that malignant acanthosis is a genodermatosis which may be associated with a genetic tendency to the development of a specific adenocarcinoma[34].

A third form, called pseudoacanthosis nigricans, occurs in obese individuals, resembles true acanthosis nigricans only superficially, and disappears with weight reduction, never being associated with cancer, except by sheer coincidence.

Acrodermatitis Enteropathica. Acrodermatitis enteropathica is a rare disease of unknown cause resulting in a syndrome consisting of alopecia, mental depression, vesico-bullous lesions occurring on the hands and feet, and about the body orifices. The disease

often accompanied by diarrhea begins in early infancy, pursues an intermittent but progressive course, and ends in death[15,20,27,45]. First defined clinically by Danbolt and Closs in the Scandinavian literature in 1942, acrodermatitis enteropathica was previously held to be a form of epidermolysis bullosa. However, *Candida albicans* has usually been found in the lesions, and a number of investigators have studied the relationship of moniliasis to this disease. Most of these workers feel that *Candida albicans* is a secondary invader, and not the etiologic agent. Schlomovitz, Dillaha, and Bloom have reported separately that they have had successful results in treatment of this disorder with Diodoquin, using 250 mg. four times daily. Recently, Hare and Schlesinger[25] presented a case of acrodermatitis enteropathica in a young girl who showed cutaneous lesions and decreased fecal tryptic activity, with a marked increase in fecal fat. Her skin lesions responded to Diodoquin only after she also received pancreatin.

Peutz-Jeghers Syndrome. The Peutz-Jeghers syndrome consists of a peculiar pigmentation of the skin and mucous membranes, seen in association with familial polyposis of the stomach, small, and large intestine. The pigmentation is in the form of brownish macules on the oral mucosa, lips, around the nose and mouth and occasionally on the hands[45]. The process is rare, 47 proven cases having been collected by Richterich van-Baerle, Byrnes, Morris, and Scheff as of July, 1955[37]. The pigmentation is important to the clinician for two reasons: these individuals frequently develop intussusception, and 15% of the cases of familial polyposis develop malignant degeneration of the polyps. The pigment consists of melanin, and melanoplakia, as Beerman and Colburn[11], and Troxall[47] point out, may occur in normal people as well as other conditions besides the Peutz-Jeghers syndrome.

The Plummer-Vinson Syndrome. Once called hysterical dysphagia by Vinson, the Plummer-Vinson syndrome has several interesting features which concern this discussion. The syndrome is characterized by microcytic, hypochromic anemia, cheilitis and atrophy of the tongue, spooning of the nails, and a peculiar dysphagia associated with a webbing phenomenon at the upper end of the esophagus[3]. Furthermore, in a series of 250 cases of cancer of the upper gastrointestinal tract studied by Ahlbom, as quoted by Hutton[28], 70% had the Plummer-Vinson syndrome. Hence, this syndrome may have greater significance than was formerly supposed. It should be noted that some authors have questioned the nature of the esophageal involvement, feeling it to be an hysterical manifestation with no demonstrable anatomic change, but Hutton[28] clearly describes the roentgenologic demonstration of the esophageal constriction and webbing.

Rosacea. Rosacea is a chronic, progressive condition, characterized by early, transitory erythema of the center of the face, which later becomes permanent, and accompanied by telangiectasia, sebaceous gland hyperplasia, and occasional ocular involvement. Rosacea is more common in women than in men, begins in early middle age, and is the subject of considerable debate among dermatologists regarding its etiology.

Rosacea has long been believed to be associated with hypoacidity, dietary inadequacies, and emotional disturbances. Stokes and Pillsbury[44], in 1930, presented a theory of a gastrointestinal mechanism for rosacea. Factors implicated were emotional stress, hypochlorhydria, and derangement of in-

testinal absorption. Other investigators have incriminated a parasite, *Demodex folliculorum*, as the etiologic agent, although this concept is not supported by critical investigation[12]. Recently, in Beerman's review[9] of the general picture of rosacea, it is pointed out that Søbye presents evidence refuting the causal relationship to rosacea of diet, endocrinopathy, infection, avitaminoses, and psychic factors. Despite the fact that various workers reach conflicting conclusions concerning the cause or causes of rosacea, most dermatologists continue to use a constitutional approach to this disorder.

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PHYSIOLOGY

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Cardiovascular and Respiratory Effects of Nicotine in Chloralose Anesthetized Cats and Dogs. CARL C. GRUHZIT, M.D., PH.D. (Department of Physiology and Pharmacology, Graduate School of Medicine, University of Pennsylvania, Philadelphia). The relative significance and sensitivity of the various mechanisms involved in the cardiovascular and respiratory responses to nicotine were studied in chloralose-anesthetized cats and dogs by comparing the effects produced by right atrial, pulmonary arterial, left ventricular and intra-aortic injections of graded doses of nicotine before and after cervical vagotomy, carotid sinus nerve section, adrenalectomy and the administration of adrenergic, cholinergic and ganglionic blocking agents. Femoral arterial and right atrial pressures were measured by means of strain gauges and recorded on a Grass electroencephalograph. Respiration was recorded on the EEG by means of a modified "Donald-Christie" apparatus.

The minimal effective right atrial dose of nicotin (0.25–4.0 μg./kg.) produced respiratory stimulation frequently accompanied by a rise in blood pressure. Slightly larger doses of nicotine (1.0–8.0 μg./kg.) injected into the right atrium produced initial respiratory depression, bradycardia and hypotension, occurring after a latent period, usually less than three seconds, followed by hyperpnea and, frequently, tachycardia and hypertension. Left ventricular injections of nicotine produced qualitatively similar effects except that the initial respiratory depression was not observed. Vagotomy alone or the administration of sodium thiopental prevented the respiratory and cardiovascular depressant effects. The hyperpnea, hypertension and tachycardia elicited by 0.25–8.0 μg./kg. nicotine were usually abolished by section of both the vagi and carotid sinus nerves, but larger doses of nicotine still produced a rise in blood pressure which could be inhibited or abolished by adrenergic or ganglionic blocking agents.

The results indicate that the hyperpnea, hypertension and tachycardia produced by moderate doses of nicotine are due primarily to the stimulation of the aortic and carotid bodies, while larger doses also stimulate the sympathetic ganglia and the adrenal medulla. The initial depressant action of nicotine is due to the stimulation of coronary and pulmonary chemoreflexes although parasympathetic ganglionic stimulation may be observed with large doses.

The Effects of Nicotine on Left Ventricular Work and Coronary Blood Flow. J. E. SCHMITTHENNER, M.D., J. B. HAFKENSCHIEL, M.D., I. FORTE, B.A., M.S., AND C. RIEGEL, PH.D., Lankenau Hospital. The effects of 30-minute nicotine infusions were compared with those of saline infusions in fifteen paired experiments using the same four anesthetized dogs (morphine, pentobarbital and dial urethane). Coronary blood flow was measured by the nitrous oxide desaturation method, and cardiac output by the direct Fick method. No significant changes were noted from the

control periods with a dosage rate of 5 μg./kg./min. In the seven experiments using 15 μg./kg./min., significant increases in mean values of left ventricular work (3.8 to 6.5 kg. M./min.) and coronary flow (82 to 135 ml./100 gm. L.V./min.) occurred. Pulse rate rose (64 to 90) more than mean arterial pressure (104 to 114). Respiratory minute volume and total body oxygen consumption were increased. The rise in left ventricular oxygen consumption (9.1 to 17.5 ml./100 gm./min.) was greater than the increase in coronary flow; however, increase in arterial hemoglobin (13.6 to 16.1 gm.) and the per cent saturation of arterial blood (86 to 94) permitted increased oxygen extraction by the left ventricle, with no significant change in the pO_2 of coronary sinus blood. Coronary resistance fell (1.4 to 0.9 units) and left ventricular mechanical efficiency was unchanged. Adrenal medulary stimulation is suggested as the major mechanism of action.

Cardio-dynamic Effects of Intracoronary Injection of Nicotine. J. W. West and S. V. Guzman, M.D. (Department of Pharmacology, University of Pennsylvania, and Department of Cardiology, Philadelphia General Hospital). The direct cardiovascular, cardiac ganglionic and cardiac receptor stimulation by nicotine on the Bezold-Jarisch reflex, coronary blood flow, myocardial contractility and cardiac electrical activity were studied in dogs under light morphine-chloralose or pentobarbital sodium anesthesia. Coronary arterial catheterization of a major branch of the left or right coronary artery via one carotid artery and cannulation of the coronary sinus via a jugular vein were accomplished under fluoroscopic guidance, while the chest remained intact. Nicotine injected in the coronary artery in doses ranging from 0.40 to 1 μg./kg. resulted in an increase in coronary blood flow of 5 to 42%. Cardiac contractility measured by means of a Walton strain gauge sutured directly to the anterior surface of the left ventricle resulted in an increase in contractility of 40 to 90%. The electrocardiographic changes consisted of lowering or inversion of the T wave, followed later by peaking of the T. All of these changes were qualitatively similar to the effects of intracoronary injection of epinephrine. Injections of nicotine in the right coronary and left circumflex branch resulted in bradycardia, cardiac block and tachycardia. All of these effects of nicotine were blocked by TEABr. Nicotine in doses of 0.2 to 2.0 μg./kg. injected into the anterior descending and circumflex branches of the left coronary artery resulted in the full Bezold-Jarisch reflex (respiratory inhibition, bradycardia, hypotension). These effects were eliminated by intracoronary injection of TEA or bilateral vagotomy. Atropine (I.V.) abolished the bradycardia but not the respiratory inhibition and hypotension. In these experiments there was no evidence of coronary vasoconstriction resulting from intracoronary injection of nicotine. The results obtained in these experiments can best be explained by the presence in the heart of parasympathetic and sympathetic ganglion-like and special receptors influenced by nicotine.

Smoking and Lung Cancer. Katharine R. Boucot, M.D., M.P.H. (Department of Preventive Medicine, Woman's Medical College of Pennsylvania) and David A. Cooper, M.D. (Department of Medicine, University of Pennsylvania School of Medicine). While the cause of lung cancer is unknown, numerous sound epidemiologic studies have shown a lower percentage of nonsmokers and a higher percentage of heavy smokers among lung cancer cases than among those without cancer.

Doll and Hill, in 1956, reported an increase in lung cancer deaths among British physicians over age 35 with increasing degrees of smoking, the 4-year death rate for heavy smokers having been 20 times that for nonsmokers. Over a follow-up period of 1 to 5 years, there have been 77 proved lung cancers among a group of 6,138 men over 45 who joined the Philadelphia Pulmonary Neoplasm Research Project. Only one cancer occurred in a nonsmoker. The group is not a random sample since the primary objective of the Project is to study the chronologic relationship between symptoms and radiologic changes in lung cancer. However, the men were unselected as to smoking habits. Cancer has occurred in 0.97% of occasional cigarette smokers ($<$ ½ pack/day), 1.72% of moderate cigarette smokers (½ to 1 pack/day), and 1.92% of heavy smokers ($>$ 1 pack/day). The occurrence of lung cancer in heavy cigarette smokers has been 15 times that for nonsmokers. While Auerbach's pathologic studies suggest a carcinogenic action of cigarette smoke, the majority of cigarette smokers do not develop cancer. The hypothesis is presented that a major relationship between smoking and lung cancer may be one of irritation predisposing to the action of the true carcinogen. Because of the consistency with which different studies by sincere investigators yield similar trends, it is suggested that, pending definitive proof, the lay public and physicians should continue to be cautioned about the hazards of smoking.

BOOK REVIEWS AND NOTICES

OCCUPATIONAL DISEASES OF THE SKIN. By LOUIS SCHWARTZ, M.D., Medical Director (Retired), U.S. Public Health Service; LOUIS TULIPAN, M.D., Emeritus Clinical Professor of Dermatology, New York University, Bellevue Post-Graduate Medical School; and DONALD J. BIRMINGHAM, M.D., Medical Director, Chief Dermatologist, Occupational Program, U.S. Public Health Service. 3rd ed. Pp. 981; 189 ills. Philadelphia: Lea & Febiger, 1957. Price, $18.00.

THIS edition of *Occupational Diseases of the Skin* has a new third author, Birmingham, instead of Peck. A revision of this text was deemed necessary because "the new chemicals and new methods of manufacture which are so rapidly and constantly being evolved, bring with them new skin hazards to workers engaged in their manufacture and in their application, as well as to the public who use products containing these chemicals." The volume has been enlarged by the addition of new features. These include: "Occupational Marks," by F. Ronchese; "Skin Hazards from Radiation in Atomic Industry, Medicine and Defense," by W. D. Norwood; and "Skin Hazards of Detergents and Surface Active Agents," by A. M. Schwartz. These indicate the up-to-date coverage. The one change which is of doubtful value to the new student is the limiting of references to those after 1943. References prior to this date are to be found only in the first and second editions. This presentation is clear, to the point, well illustrated, adequate and well indexed. As it stands, it is a good source book for all interested in occupational dermatology.

H. B.

CLINICAL ELECTROCARDIOGRAPHY. INTERPRETATION ON A PHYSIOLOGIC BASIS. By MANUEL GARDBERG, M.D. (with chapters by R. ASHMAN, I. L. ROSEN, L. LEVY, II), Louisiana State University School of Medicine and Touro Infirmary, New Orleans. Pp. 315; 259 ills. New York: Paul B. Hoeber, Inc., 1957. Price, $12.75.

THERE are available many texts in electrocardiography. The author of this text has succeeded well in what the subtitle implies. Many electrocardiographers still express opinions based on memorizing empirical patterns; this state will have been overcome after study of this text. The many original drawings will be of great value to the reader in helping him to visualize and understand the distribution of electrical forces and the formation of the various complexes. To the extent to which this is possible, electrocardiographic phenomena are presented in terms of the frontal plane and spatial loops, and the QRST and gradient vectors; and the understanding of the precordial leads is enhanced by the solid angle derivations. Particularly interesttion is the presentation of E.C.G. changes occurring as the result of food, smoking, and exercise; and with respect to the latter, fallacies of the empirical criteria for S–T–T changes are stressed. Also to be commended is the critical attitude in evaluating serial changes in persons whose original tracings are abnormal. The great variety of the positions of the heart and how they affect the shape of the frontal plane leads is instructively presented. Many tracings from actual patients illustrate the points under discussion; in this connection, mention should be made that the QRS portions have sometimes been redrawn and that the study of serial tracings is occasionally made difficult because, in the course of mounting, the base line levels vary, and that relatively few cases have close correlation with detailed postmortem findings. Nearly 70 pages are devoted to the basic principles; then follow chapters on injury; ischemia, left and right ventricular hypertrophy, left and right bundle branch block, coronary disease, disturbances of cardiac mechanism (with discussion of excitability, refractoriness and conduction), the effect of drugs, electrolytes and metabolic disturbances, a short consideration of etiologic types of heart disease, and finally vectorcardiography and spatial vectorelectrocardiography.

H. B.

PROPRIOCEPTIVE NEUROMUSCULAR FACILITATION (PATTERN AND TECHNIQUES). By MARGARET KNOTT, B.S., Head Physiotherapist, and DOROTHY E. VOSS, B.ED., Assistant Head Physiotherapist, California Rehabilitation Center, Vallejo, California. Pp. 135; 38 ills. (By Helen Drew). New York: Paul B. Hoeber, Inc., 1956. Price, $5.50.

THIS manual has been prepared by two physiotherapists who have applied the techniques of proprioceptive neuromuscular facilitation, which was first developed at the

Kabat-Kaiser Institute, to the important problem of rehabilitation. Those techniques are used as a means of stimulating and strengthening the response of a neuromuscular mechanism.

The authors have made available the basic information necessary to the learning of these techniques by clear descriptions which are reinforced by profuse and excellent illustrations. The material is divided into Part I: Technique of Proprioceptive Neuromuscular Facilitation. Part II: Patterns of Facilitation. Part III: Evaluation and Treatment Progress and Part IV: Reference Tables.

This excellent manual will prove invaluable to all physiotherapists and to those interested in rehabilitation regardless of the specialty.

M. S.

Urological Surgery. By Austin Ingram Dodson, M.D., Medical College of Virginia. 3rd ed. Pp. 868; 664 ills. St. Louis: C. V. Mosby Co., 1956. Price, $20.00.

The third edition of this excellent book on surgical technique brings up-to-date many of the advances being constantly made in surgery of the urinary tract.

The book is an expression of the author's own experience during many years in the practice of urologic surgery. A number of chapters have been dropped, many rewritten and a number of new subjects discussed. One deals with urologic rehabilitation of the paraplegic patient, another with adrenal surgery.

Unfortunately, surgery involving the use of the ileum in urology is not discussed. This currently popular topic is too recent a development to have been included in this very worthwhile text.

L. K.

Principles of Urology. By Meredith F. Campbell, M.D., F.A.C.S., Emeritus Professor of Urology, New York University. Pp. 622; 319 ills. Philadelphia: W. B. Saunders Company, 1957. Price, $9.50.

Dr. Campbell is the author of two previous texts: his well known *Clinical Pediatric Urology*, a standard in this field; and, more recently a most complete three volume *Urology*. His most recent contribution is a well organized text on the principles of urology which meets the standard of his previous work.

The book is logically organized into broad pathological subdivisions of urology, with emphasis on the effects of disease on the whole urinary tract. Two sections, on neuromuscular uropathy and on diseases of the adrenal glands, are outstanding. In many similar texts, these are missing or inadequately covered.

Dr. Campbell's text, as his previous works, will undoubtedly take its place among the leading urological basic textbooks. It is to be recommended for use by the student, resident and practitioners in the field of urology.

K. C.

Positioning in Radiography. By K. C. Clark, M.B.E., F.S.R. 7th ed. Pp. 655; 2150 ills. London: Percy Lund, Humphries & Co. Ltd.; New York: Grune & Stratton, Inc., 1956. Price, $29.00.

This volume has been in continuous service in our Department since its first edition in 1939, and has proved itself invaluable as a complete reference work on radiographic technique. It is therefore with enthusiasm that we welcome this latest edition enhanced with 2,150 illustrations, which completely clarify every known radiographic position and technique.

Though modestly titled "Positioning in Radiography," the work is a complete atlas and treatise covering every facet of radiographic technique. It is medical as well as technical, containing a wealth of pathologic material, and this latest edition brings it up to the minute in latest techniques applied in the various specialties, including cineradiography, photofluorography (microradiography), macroradiography, image intensification and radiography of the cardiovascular system.

G. B.

Rheumatic Diseases, Rheumatism and Arthritis. By Heinrich G. Brugsch, M.D., Tufts University Medical School. Pp. 330; 58 ills. Philadelphia: J. B. Lippincott Company, 1957. Price, $10.00.

In this volume Dr. Brugsch attempts the well nigh impossible task of presenting the whole field of rheumatology without the aid of co-authors. Of necessity the scope of such a work falls between that of a purely introductory handbook and that of an authoritative reference work. Whether a place exists for this type of book may be questioned, but the skill which the author displays in selecting his material and in dealing with it from the point of view of general internal medicine is commendable. Those with a wide experience with the rheumatic diseases may feel a certain lack of emphasis and perspective in the arrangement of parts of the text, and

the novice may feel the need of fuller directions in the technique of drug therapy as applied to a given case. But within the limits which he has set himself Dr. Brugsch has succeeded in presenting a personal compilation of the known facts of rheumatology. (A comprehensive Bibliography is provided for direction in studying the more controversial aspects of the field.) J. L.

DISEASES AND DISORDERS OF THE COLON. By ANTHONY BASSLER, M.D., Consulting Gastroenterologist, New York Polyclinic Medical School and Hospital. Pp. 217; 79 ills. Springfield, Ill.: Charles C Thomas, 1957. Price, $6.75.

THE author, who has had a long and vast experience in the practice of gastroenterology, has attempted to present to the practitioner a book to serve as a guide in diagnosis and treatment of diseases of the colon. The style of writing is simple and direct, made more so by the elimination of a Bibliography. The author's forte is in diagnosis and in this discipline he makes some useful suggestions. However, there are few who would agree with his concept of "chronic appendicitis." There are even fewer who would accept his classification of toxic colitis which he divides into indolic or putrefactive type and sacchrobutyric or fermentative type. Most clinicians prefer the terminology of "irritable colon." Physiology is essentially omitted and where it is included, it is often incomplete and inaccurate. The pharmacologic recommendations are decades behind current concepts of therapy. There are few surgeons, let alone internists, who would agree with the author's statement that, "In the presence of obstruction it is not necessary to know the exact cause of the obstruction but to operate as quickly as possible and operation best discloses the cause." Even the author contradicts this state- This book cannot be recommended.

S. L.

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